Value of Child-Turcotte-Pugh Score in Prediction of Treatment Response in “Difficult to Treat” Chronic HCV Cirrhotic Patients

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Abstract

Background and aim: The direct-acting antivirals (DAAs) treatment has greatly improved sustained virologic response (SVR) in chronic non-cirrhotic hepatitis C virus (HCV) patients and to less extent in those with cirrhosis. There is a stressing need for predicting the outcome of DAAs treatment especially in “difficult to treat” patients. This work aimed to study the value of the Child-Turcotte-Pugh (CTP) score in the prediction of treatment outcome with DAAs in “difficult to treat” chronic HCV patients. Materials and methods: A retrospective cohort study was conducted where files of 120 “difficult to treat” patients were randomly selected from the follow-up clinic. Patients’ data were collected before and after treatment including history taking, clinical examination, laboratory investigations, and abdominal ultrasonography. Child-Turcotte-Pugh (CTP) scores were calculated. Results: There was no significant difference in mean Child score between patients with and without SVR before treatment, while this difference became significant after treatment. The patients without complications showed a highly significant decrease in their mean Child score after treatment, while patients with complications did not show any significant differences. Conclusion: The baseline Child-Turcotte-Pugh score cannot predict the treatment response of DAAs in “difficult to treat” chronic HCV patients, but it is significantly associated with the occurrence of complications.

Keywords
Hepatitis C, Child Score, Cirrhosis

1. Introduction

Hepatitis C virus (HCV) infection is a very dreadful widely but unevenly distri-
but a global health problem. According to the World Health Organization (WHO), about 150 million people worldwide are already infected with HCV [1]. Chronic HCV infection can be complicated with liver cirrhosis and eventual further complications including liver decompensation, end-stage liver disease and hepatocellular carcinoma (HCC) stressing the need for liver transplantation. Chronic HCV is also associated with an increased risk of liver-related mortality [2] [3] [4].

Many therapeutic trials were conducted over more than two decades to achieve a sustained virologic response (SVR). SVR is reached when HCV-RNA becomes undetectable 12 weeks after the end of treatment (SVR12). Achieving SVR is associated with a decrease in the incidence of liver cancer (HCC) and improved survival in HCV patients whether cirrhotic or non-cirrhotic [5] [6] [7]. The recent direct-acting antiviral agents (DAAs) have markedly improved the SVR rates and gave a great therapeutic chance to a wide category of patients including those with contraindications or low SVR rates to Peg-IFN based antiviral therapy regimens [8] [9]. However, a great concern is still present about some patients showing a marked deterioration of liver function in spite of effective viral clearance. In such patients, the prediction of benefits of DAAs was not duly established so the outcome of treatment was not satisfactory. In this situation, the evaluation of predictors of treatment outcome is mandatory to allow such difficult-to-treat patients making the greatest benefit of treatment, not only by viral eradication but also by significant improving hepatic function [10] [11].

Various host and viral factors were implicated for the prediction of treatment outcome of HCV infection especially with the recent emergence of the pan-genotypic oral DAAs. Multiple variables such as age, gender, race, insulin resistance, body mass index, steatosis, advanced fibrosis stage, viral load, and HCV genotype were tried with interferon-based therapies for prediction of treatment outcome. They were found to be associated with non-response to therapy. However, these predictive variables may be not such important with DAAs as they were before with interferon [12] [13] [14] [15]. Other sets of suggested predictive variables, such as age, Child-Turcotte-Pugh (CTP) score, and platelet count, were tried with oral DAAs. Some authors considered CTP score as a system for deciding the strength of treatment, predicting the prognosis, deciding the necessity for liver transplantation and survival rate in chronic liver disease, mainly cirrhosis. The CTP score adopts multiple variables including serum albumin level, serum bilirubin level, ascites, hepatic encephalopathy and the International Normalizing Ratio (INR). Old age, CTP class B, low platelet count, and cirrhosis were found to be associated with non-response to DAAs therapy [16] [17]. Other studies were conducted using CPT score to assess the outcome of DAAS in HCV cirrhotic patients yet failing to prove a well-defined predicting ability of that score [16] [17] [18]. The aim of this work was to study the value of Child-Turcotte-Pugh score in the reliable prediction of treatment outcome with DAAs in “difficult to treat” chronic HCV patients.
2. Patients and Methods

A retrospective cohort study was conducted at Tropical Medicine Department, Zagazig University Hospitals from May 2018 to December 2018. This study was conducted on 120 “difficult to treat” chronic HCV cirrhotic patients. The files of the patients were selected randomly from the follow-up clinic until the completion of the sample size. The sample size was decided according to the Institutional Review Board (IRB) and statistical specialists.

**Inclusion criteria:**
Patients were selected according to the Supreme Council and the National Committee for Control of Viral Hepatitis (NCCVH) updated treatment protocol December 2016 [19]:
- HCV RNA positivity.
- Age ≥ 18 years.
- Selection of “difficult to treat” HCV Patient including one or more of the following criteria:
  - Serum albumin ≤ 3.5 g/dl
  - PEG-IFN treatment-experienced.
  - Child A and B classes.
  - Total serum bilirubin ≥ 1.2 mg/dl.
  - INR ≥ 1.2.
  - Platelet < 150,000/mm$^3$.

**Exclusion criteria:**
Patients were excluded if they have one or more of these criteria:
- Child C cirrhotic patients (Child score ≥ 10)
- Pregnancy or inability to use effective contraception.
- Inadequately controlled diabetes mellitus (HA1C > 9).
- Platelet count < 50,000/mm$^3$
- HCC, except 6 months after intervention aiming at a cure with no evidence of activity by dynamic imaging (CT or MRI).
- Extra-hepatic malignancy except after two years of disease-free interval.

**Methods:**
The patients had been already treated by Sofosbuvir (400 mg)/day + Daclatasvir (60 mg)/day + Ribavirin for 12 weeks. The starting dose of ribavirin is 600 mg/day. Trials were done to reach a dose of 1000 mg/day based on individual patient tolerability. The data of all patients were collected twice, before treatment and the 12 weeks after the end of treatment. The data included:
- Detailed history taking and clinical examination.
- Laboratory investigations including Complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum albumin, alpha-fetoprotein, international normalized ratio (INR), serum creatinine and HCV RNA PCR.
- Abdominal ultrasonography.
- Child-Turcotte-Pugh score was calculated pre and post-treatment according to Table 1.
Table 1. Child-Pugh scoring system.

| Measurements       | Score       |
|--------------------|-------------|
|                    | 1           | 2               | 3               |
| Encephalopathy     | None        | Grade I-II      | Grade III-IV    |
| Ascites            | None        | Mild            | Moderate to tense|
| Bilirubin (mg/dL)  | 1 - 2       | 2 - 3           | >3              |
| Albumin (g/dL)     | >3.5        | 2.8 - 3.5       | <2.8            |
| INR                | <1.7        | 1.7 - 2.20      | >2.20           |

Class A: 5 - 6 points; Class B: 7 - 9 points; Class C: 10 - 15 points (17).

Statistical Analysis

Data were checked, entered and analyzed using SPSS 15 for Windows. Data were expressed as mean ± SD for the quantitative variable, number, and percentage for qualitative one. Chi-square (X²) or t-test, paired t-test, McNemar’s test or Stuart-Maxwell test were used when appropriate. P < 0.05 was considered significant. P < 0.001 was considered highly significant.

3. Results

A total number of 120 patients who were categorized as “difficult to treat” were included in this retrospective cohort study. Their files were selected randomly from the follow-up clinic until the completion of the sample size from May 2018 to December 2018.

Males:females’ ratio was about 59.2%:40.8% of patients. The mean age was about 50.52 years and 10.8% only had prior HCV treatment. Their mean AFP and HCV RNA levels were 23.8 ng/ml and 6.25 million IU/ml respectively (Table 2).

After treatment, there was a highly significant decrease in the following lab measurements; Hb, WBCs, ALT, AST and TSB, while S. albumin significantly increased. However, others showed no significant changes (Table 3).

After treatment, 94.16% of patients showed SVR and 94.16% did not show any complications. Seven patients (5.83%) were complicated by variceal bleeding (2 cases), grade 2 hepatic encephalopathy (2 cases) and 3 cases show HCC after treatment (Table 4).

There was a highly significant upgrading of Child classes in patients with SVR where Child classes were changed from B to A after treatment in about 21.2% of patients. On the other hand, Child classes were not affected by treatment in patients without SVR (Table 5).

There was a non-significant difference in mean Child score between patients with and without SVR before treatment, while this difference became significant after treatment. There was a highly significant decrease in the mean Child score in patients with SVR and an unchanged score of patients without SVR after
Table 2. Basic characteristics of the studied patients.

| Demographic data          | All patients (N = 120) |
|---------------------------|------------------------|
|                           | No.        | %        |
| Gender                    |            |          |
| Male                      | 71         | 59.2%    |
| Female                    | 49         | 40.8%    |
| Age (years)               |            |          |
| Mean ± SD                 | 50.52 ± 8.48|          |
| Median (range)            | 54 (29-67) |          |
| AFP (ng/ml)               |            |          |
| Mean ± SD                 | 23.80 ± 18.40|        |
| Median (range)            | 16 (9-97)  |          |
| HCV RNA (x10^6 IU/ml)     |            |          |
| Mean ± SD                 | 6.25 ± 4.17|          |
| Median (range)            | 7 (1-17)   |          |
| Prior HCV treatment       |            |          |
| No                        | 107        | 89.2%    |
| Yes                       | 13         | 10.8%    |

AFP: Alpha feto protein.

Table 3. Comparison between pre-treatment and post-treatment laboratory results among the studied patients.

| Laboratory results     | Pre-treatment (N = 120) | Post-treatment (N = 120) | Test \( p \)-value |
|------------------------|-------------------------|--------------------------|-------------------|
| Hemoglobin (g/dl)      |                         |                          |                   |
| Mean ± SD              | 11.83 ± 1.35            | 11.19 ± 1.24             | −6.208 <0.001 (HS) |
| Median (range)         | 12.80 (10 - 15)         | 12 (9 - 14.40)           |                  |
| WBCs (x10^3/mm^3)      |                         |                          |                   |
| Mean ± SD              | 6.11 ± 2.18             | 5.91 ± 2.03              | −3.109 0.002* (S) |
| Median (range)         | 6 (3 - 11)              | 5.20 (2.70 - 10)         |                  |
| Plt count (x10^3/mm^3) |                         |                          |                   |
| Mean ± SD              | 100.18 ± 26.18          | 100.84 ± 30.26           | −0.368 0.713 (NS) |
| Median (range)         | 100 (51 - 149)          | 30.26 (42 - 170)         |                  |
| AST (IU/L)             |                         |                          |                   |
| Mean ± SD              | 46.17 ± 20.22           | 36.25 ± 12.56            | −5.469 <0.001 (HS)** |
| Median (range)         | 41 (12 - 98)            | 35 (12 - 78)             |                  |
| ALT (IU/L)             |                         |                          |                   |
| Mean ± SD              | 38.56 ± 18.99           | 30.61 ± 13.29            | −3.959 <0.001 (HS)** |
| Median (range)         | 37.2 (13 - 80)          | 29.1 (11 - 80)           |                  |
Continued

| TSB (mg/dl) | Mean ± SD | Median (range) | P-value |
|-------------|-----------|----------------|---------|
| 2.22 ± 0.52 | 1.98 ± 0.51 | -4.400 <0.001 (HS)** |
| Albumin (g/dl) | Mean ± SD | Median (range) | P-value |
| 3.33 ± 0.24 | 3.45 ± 0.27 | -6.975 <0.001 (HS)** |
| INR | Mean ± SD | Median (range) | P-value |
| 1.34 ± 0.13 | 1.32 ± 0.10 | -1.769 0.077 (NS) |
| Serum creatinine (mg/dl) | Mean ± SD | Median (range) | P-value |
| 1.25 ± 0.13 | 1.25 ± 0.12 | -0.362 0.717 (NS) |

1Wilcoxon signed ranks test. *significant. NS: non-significant. **Highly significant. Plt: platelets. WBCs: white blood cells. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. TBS: total serum bilirubin.

Table 4. Outcome of treatment of the studied patients.

| Outcome of treatment | All patients (N = 120) |
|----------------------|-----------------------|
|                      | No. | %               |
| SVR                  |     |                 |
| No                   | 7   | 5.83%           |
| Yes                  | 113 | 94.16%          |
| Complications        |     |                 |
| No                   | 113 | 94.16%          |
| Yes                  | 7   | 5.83%           |

SVR: sustained virologic response.

Table 5. Comparison between patients with and without SVR as regard pre- and post-treatment Child class.

| Child score | With SVR (N = 113) | Without SVR (N = 7) | Test† | P-value |
|-------------|--------------------|---------------------|-------|---------|
|             | No. | %    | No. | %    |       |        |
| Pre-treatment class |     |       |      |       |       |        |
| Child A     | 62  | 54.9%| 3   | 42.9%| 0.408 | 0.659 (NS) |
| Child B     | 51  | 45.1%| 4   | 57.1%|       |         |
| Post-treatment class |     |       |      |       |       |        |
| Child A     | 86  | 76.1%| 3   | 42.9%| 3.081 | 0.112 (NS) |
| Child B     | 27  | 23.9%| 4   | 57.1%|       |         |
| Test*       | 16.056 | 1.000 |      |       | <0.001** | 0.317 (NS) |
| P-value     | <0.001** | 0.317 (NS) |      |       |         |

†Chi-square test. †McNemar’s test. NS: non-significant. **highly significant. SVR: sustained virologic response.
treatment (Table 6).

The mean Child score showed a significant difference between patients with and without complications before treatment and a highly significant difference after treatment. The patients without complications showed highly significant decrease in their mean Child score after treatment, while patients with complications did not show any significant differences (Table 7).

4. Discussion

Egypt has the highest worldwide prevalence of HCV [20]. Genotype 4 represents the most common genotype of HCV in Egypt accounting for about 93% of the burden of HCV infection [21]. A dramatic change has evolved in the treatment of HCV after the introduction of DAAs shifting the treatment of chronic HCV to a new level of effective potency and high safety [22]. DAAs were useless in some patients and others have been deteriorated or even died on treatment. Therefore, prediction of the outcome of DAAs treatment is a fundamental step

Table 6. Comparison between patients with and without SVR as regard pre- and post-treatment Child score’s mean.

| Child score | With SVR (N = 113) | Without SVR (N = 7) | Test‡ | P-value |
|-------------|-------------------|---------------------|-------|---------|
| Pre-treatment score |
| Mean ± SD | 6.62 ± 0.79 | 7.21 ± 1.31 | −1.091 | 0.275 (NS) |
| Median (range) | 7 (6 - 9) | 6 (6 - 9) | |
| Post-treatment score |
| Mean ± SD | 6.14 ± 0.92 | 7.19 ± 1.29 | −2.004 | 0.045* |
| Median (range) | 7 (5 - 9) | 6 (6 - 9) | |
| Test* | −5.758 | 1.000 | |
| P-value | <0.001** | 0.317 (NS) | |

*Significant. **highly significant. NS: non-significant. ‡Mann Whitney U test. *Wilcoxon signed ranks test.

Table 7. Comparison between patients with and without complications as regard pre- and post-treatment Child score’s mean.

| Child score | Without complication (N = 113) | With complications (N = 7) | Test‡ | P-value |
|-------------|-------------------------------|--------------------------|-------|---------|
| Pre-treatment |
| Mean ± SD | 6.54 ± 0.71 | 8.21 ± 0.82 | −3.467 | 0.001* |
| Median (range) | 6 (6 - 9) | 8 (7 - 9) | |
| Post-treatment |
| Mean ± SD | 6.07 ± 0.81 | 8.41 ± 0.88 | −3.771 | <0.001** |
| Median (range) | 6 (5 - 8) | 9 (7 - 9) | |
| Test* | −5.962 | −1.000 | |
| P-value (Sig.) | <0.001** | 0.317 (NS) | |

**highly significant. *significant; NS: non-significant. ‡Mann Whitney U test. *Wilcoxon signed ranks test.
to make sure that SVR and clearance of HCV will be achieved not only effectively but also safely [23] [24].

This work aims to study the value of Child-Turcotte-Pugh score in the reliable prediction of treatment outcome with DAAs in “difficult to treat” chronic HCV patients.

In this study, the course of treatment resulted in an overall 94.16% achievement of sustained virologic response at week 12 (SVR12) with 100% (n = 13) for treatment-experienced (interferon and ribavirin for 48 weeks) patients. This result agrees with many Egyptian and American studies, which confirm the efficacy of DAAs in the management of HCV in Egypt [25] [26] [27] [28]. However, the reported SVR12 of treatment-experienced patients is higher than other studies, which may be because some patients who included were Child A who usually obtain significantly higher SVR than Child B/C [29].

Hemoglobin level decreased significantly at weeks 12 after treatment but there was no requirement for dose reduction or stopping treatment. This coincides with the results of Deterding et al. who reported a decrease in baseline hemoglobin during treatment by almost 2 g/dL. Ribavirin and DAAs can cause anemia as a side effect [30].

In this study, there was a significant reduction in AST and ALT level and improvement of liver function parameters including albumin and bilirubin are improved in the majority of patients. These results agree with those of Deterding et al., Mehta et al. and Charlton et al. where they studied different genotypes with different combinations of DAAs at week 12 [30] [31] [32]. These results prove the role of DAAs’ in improving necro-inflammation in patients with chronic HCV infection.

The SVR 12 rates describe the virologic response, while changes in CTP score describe the clinical response seen in patients 12 weeks after the end of treatment. In this study, there was a highly significant upgrading of Child class B to A in about 21.2% of patients with SVR. This result is quite consistent with that of Deterding et al. who recorded improving CPT scores in 25% of studied patients [30].

In this study, before treatment, mean Child score in patients who reported complications during the treatment (8.2 ± 0.8) was significantly higher when compared with patients without complications (6.5 ± 0.7) indicating that the high Child score is a good predictor of the occurrence of complication. However, because of the small number of patients with complications (n = 7), the exact predictive cut off value of Child score cannot be calculated by the specific statistical tests used for this purpose. This result agrees to some extent with that of Manns et al. who observed that the patients with baseline MELD score < 15 reported more improvement of their MELD and Child scores after treatment and rarely develop complications unlike those with baseline MELD score ≥ 15 [33].

After treatment, three cases of hepatocellular carcinoma (HCC) were reported in this study. This result agrees with that of Deterding et al. with DAAs induced
SVR - and Van der Meer *et al.* but with interferon-induced SVR. These results prove that although DAAs may improve liver function parameters in chronic HCV patients, HCC may still develop [30] [31] [32] [33] [34]. These findings stress the need for careful monitoring for HCC even if HCV RNA is negative.

In the current study, before treatment, mean Child score in patients who achieved SVR did not show a significant difference when compared with patients who did not achieve SVR indicating that the scores cannot be used as predictors of response to DAAs. This result is not matching with that of Carrillo *et al.* (2017) who reported that decompensated cirrhosis (CTP B/C) at baseline was associated with lower rates of virologic response compared with patients with less advanced cirrhosis (CTP A) [28]. The limitations in our study included small sample size, exclusion of patients with Child score ≥ 10 as those patients are managed in a higher tertiary center with more facilities.

5. Conclusion

The baseline Child-Turcotte-Pugh score cannot predict the treatment response of DAAs in “difficult to treat” chronic HCV patients, but it is significantly associated with the occurrence of complications.

**Ethical Approval**

The research protocol was approved by the Institutional Review Board (IRB), the ethical committee of University Hospitals.

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None.

**Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this paper.

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