MELD Score as a Predictor of Treatment Response of 'Difficult to Treat' Chronic HCV Patients

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Background and study aim: The introduction of direct acting antiviral agents shifted the management of chronic hepatitis C virus (HCV) infection to a new level. Pretreatment predictors of benefit are needed to help the selection of patients for treatment. The aim of this work is to study if Model for End Stage Liver Disease (MELD) score can be reliably used as a predictor of response to treatment with direct acting antivirals (DAAs) in 'difficult to treat' chronic HCV patients.

Patients and Methods: This is a retrospective study where files of 91 "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. MELD and Child-Turcotte-Pugh (CTP) scores were calculated.

Results: After treatment, MELD score was significantly improved in 28.6% of patients, remained stable in 57.1% and worsened in 14.3%. MELD score was significantly higher among patients with complications than those without complications before and after treatment. No significant difference was detected between patients with and without sustained virologic response (SVR) as regard MELD score changes after treatment.

Conclusion: Baseline MELD score cannot predict the response to treatment of "difficult to treat" chronic HCV patients but can predict the occurrence of complications.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major health problem affecting more than 170 million infected individuals worldwide. Liver cirrhosis is a real threat in 2–35% of the patients after 20–25 years of chronic infection **[1]**. The classical treatment for HCV infection was the dual therapy with pegylated interferon (Peg-IFN) α-2a or -2b combined with the guanosine analog ribavirin giving sustained virologic response (SVR) rate of only about 50% **[2]**. A new era of direct acting antivirals (DAAs), with SVR rate of about 90%, has emerged. Multiple regimens with various combinations of these drugs, without the use of IFN, proved to be effective and well tolerated, even among patients with advanced liver disease **[3]**.

Despite the poor treatment outcome in patients with decompensated cirrhosis (Child-Pugh B/C) compared to patients with compensated cirrhosis (Child-Pugh A), safety issues regarding the use of DAAs among those patients with the most advanced liver disease have arisen **[4]**. Successful treatment of patients with decompensated liver disease due to HCV has two potential benefits. First, it could result in resolution of complications of end-stage liver disease and improve survival resulting in delisting patients awaiting liver transplantation. Second, perhaps successful treatment of HCV could result in better post-transplant outcomes **[5]**.

Decompensation is the presence of at least one complication of end-stage liver disease including but not limited to hepatic encephalopathy, ascites or

bleeding from esophagogastric varices. **[6]**. The Model for End-stage Liver Disease (MELD) is a validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR). In patients with cirrhosis, an increasing MELD score is associated with increasing severity of hepatic dysfunction and the three-month mortality risk **[7]**. Baseline MELD score can predict the risk of hepatic decompensation during IFN and antiviral therapy helping the decision making in HCV patients with advanced liver cirrhosis **[8]**. Several studies revealed improving MELD score after DAAs therapy in some patients with advanced HCV-associated liver cirrhosis **[9,10]**.

The aim of this work is to study if MELD score can be reliably used for prediction of response to treatment with DAAs in 'difficult to treat' chronic HCV patients.

PATIENTS AND METHODS

A retrospective cohort study was conducted as a collaborate work between Tropical Medicine Department, Faculty of Medicine, Zagazig University and Viral Hepatitis Treatment Unit, Al Ahrar Teaching Hospital. Ninety- one patients who were selected and categorized as "difficult to treat" were included in this study. Their files were randomly selected from the follow up clinic - in Al Ahrar hospital- till the completion of sample size from July 2017 to January 2018.

Inclusion criteria:

According to Supreme Council and NCCVH 2016

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

Criteria of difficult to treat HCV Patient including one or more of the following:

- Serum albumin <3.5 g/dl
- Total serum bilirubin > 1.2 mg/dl
- INR >1.2
- Platelet <150,000 /mm^3
- PEG-IFN treatment experienced.
- Child A and B classes.

Exclusion criteria:

- Child C cirrhotic patients (Child score ≥ 10)
- Platelet count < 50,000 /mm3
- HCC, except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI).
- Extra-hepatic malignancy except after two years of disease-free interval.
- Pregnancy or inability to use effective contraception.
- Inadequately controlled diabetes mellitus (HA1C>9).

Methods:

Data of all patients were collected before treatment and after 12 weeks of the end of treatment. The data included:

- History.
- Clinical examination.
- Laboratory investigation including complete blood count (CBC), liver function test, international normalized ratio (INR), serum creatinine, Alpha feto protein, HCV RNA PCR and Abdominal ultrasonography.
- After collection of these data MELD and Child-Turcotte- Pugh (CTP) scores were calculated pre and post treatment.

The original mathematical formula for MELD is:

MELD = 3.78 × log [serum bilirubin (mg/dL)] + 11.2 × log [INR]+ 9.57 × log [serum creatinine (mg/dL)] + 6.43 × (0 if cholestatic or alcoholic & 1 if others).The score can be calculated on handheld computing devices, and is available at www.mayoclinic.org **[11]**.

Child -Turcotte- Pugh score:

It was calculated according to Brown et al **[12]**.

Table (1): Child -Turcotte- Pugh scoring system.

Child-Turcotte-Pugh score			
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

Treatment regimen of "difficult to treat group" is Sofosbuvir (400 mg)/ day + Daclatasvir (60mg)/ day + Ribavirin for 12 weeks. The starting dose of ribavirin is 600mg/day. Trials were done to reach a dose of 1000 mg/day based on the individual patient tolerability.

Statistical analysis

Data were checked, entered and analyzed using SPSS 15 for Windows. Data were expressed as mean ± SD for 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 high significant.

RESULTS

Ninety- one patients who were categorized as "difficult to treat" were included in this study. Their files were selected randomly from the follow up clinic till the completion of sample size from July 2017 to January 2018.

59.3% of patients were males and 40.7 % were females. The mean age was 53.52 (53.52 ± 8.48) years and 11% only had prior HCV treatment. AFP level was 23.90 ± 18.40 ng/ml and HCV RNA level was 6.35 ± 4.17 million IU/ml (Table 2).

After treatment, MELD score improved in about 28.6% of patients, remained stable in 57.1 % and worsen in 14.3 % (Table 3).

There was no significant difference in the mean values of MELD score between patients with and without SVR before treatment and also after treatment (Table 4).

MELD score was improved in 27.9% of patients who had SVR. Despite that 40% of patients without SVR showed improvement of their MELD scores. There were no significant differences between both groups regarding percentage of improved, stable and worsen cases (Table 5).

MELD score's mean was higher among patients with complications when compared with those without complications before and after treatment with significant statistical differences. The patient without complications showed highly significant decrease in their mean MELD after treatment, while patients with complications showed non-significant increase of their mean MELD score. Five patients (5.5%) were complicated by variceal bleeding (one case), hepatic encephalopathy grade 2 (one case) and HCC (one case) (Table 6).

In patients without complications, MELD scores were improved in 30.2% and worsen in about 10.5%, while in patients with complications; MELD scores did not improve in any one and worsen in 80% with highly significant difference (Table 7).

Table (2): Basic characteristics of the studied patients

Demographic data	All patients (N=91)	
	No.	%
Gender		
Male	54	59.3%
Female	37	40.7%
Age (years)		
Mean ± SD	53.52 ± 8.48	
Median (range)	56 (29 – 67)	
AFP (ng/ml)		
Mean ± SD	23.90 ± 18.40	
Median (range)	17 (8 – 97)	
HCV RNA ($x10^6$ iu/ml		
Mean ± SD	6.35 ± 4.17	
Median (range)	6 (1 – 17)	
Prior HCV treatment		
No	81	89%
Yes	10	11%

AFP: Alpha fetoprotein

Table (3): Change in MELD score among the studied patients

Change in MELD score	All patients (N=91)	
	No.	%
Improved	26	28.6%
-4	1	1.1%
-3	12	13.2%
-2	11	12.1%
-1	2	2.2%
Stable	52	57.1%
Worsened	13	14.3%
+1	7	7.7%
+2	6	6.6%

Table (4): Comparison between patients with and without SVR as regard pre- and post-treatment MELD score's mean

MELD score	With SVR (N=86)	Without SVR (N=5)	Test‡	P-value
Pre-treatment score				
Mean ± SD	14.72 ± 2.06	15.60 ± 3.13	-0.915	0.360 (NS)
Median (range)	15 (11 – 20)	17 (11 – 19)		
Post-treatment score				
Mean ± SD	14.23 ± 2.09	15 ± 3.67	-0.390	0.697 (NS)
Median (range)	14 (11 – 22)	14 (11 – 21)		
Test•	-3.394	-0.816		
p-value (Sig.)	0.001 *	0.414 (NS)		

‡ Mann Whitney U test. • Wilcoxon signed ranks test.
NS significant. * Significant.

Table (5): Comparison between patients with and without SVR as regard MELD score changes after treatment

MELD score change	With SVR (N=86)		Without SVR (N=5)		Test‡	P-value
	No.	%	No.	%		
Improved	24	27.9%	2	40%	0.635	0.728 (NS)
Stable	50	58.1%	2	40%		
Worsen	12	14%	1	20%		
-4	1	1.2%	0	0%	2.756	0.839 (NS)
-3	11	12.8%	1	20%		
-2	10	11.6%	1	20%		
-1	2	2.3%	0	0%		
0	50	58.1%	2	40%		
+1	7	8.1%	0	0%		
+2	5	5.8%	1	20%		

‡ Chi-square test. NS significant.

Table (6): Comparison between patients with and without complications as regard pre- and post-treatment MELD score's mean

MELD score	Without complications (N=86)	With complications (N=5)	Test‡	P-value
Pre-treatment				
Mean ± SD	14.59 ± 2	17.80 ± 1.92	-2.859	0.004 *
Median (range)	14 (11 – 20)	18 (15 – 20)		
Post-treatment				
Mean ± SD	13.98 ± 1.78	19.20 ± 2.68	-3.428	0.001 *
Median (range)	14 (11 – 19)	19 (15 – 22)		
Test•	-4.011	-1.890		
P-value	<0.001 **	0.059 (NS)		

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

Table (7): Comparison between patients with and without complications as regard MELD score changes after treatment

MELD score change	Without complications (N=86)		With complications (N=5)		Test‡	P-value
	No.	%	No.	%		
Improved	26	30.2%	0	0%	18.782	<0.001 **
Stable	51	59.3%	1	20%		
Worsen	9	10.5%	4	80%		
-4	1	1.2%	0	0%	26.718	<0.001 **
-3	12	14%	0	0%		
-2	11	12.8%	0	0%		
-1	2	2.3%	0	0%		
0	51	59.3%	1	20%		
+1	6	7%	1	20%		
+2	3	3.5%	3	60%		

‡ Chi-square test. ** highly significant.

DISCUSSION

Chronic hepatitis C virus infection is a major health issue worldwide. It is the leading cause of liver-related morbidity and mortality in Egypt and one of the most common indications for liver transplantation **[13]**. Pretreatment predictors of benefit are needed to guide patient selection for therapy and, more importantly, identify a group of patients in whom therapy is useless and who should undergo liver transplantation and DAAs therapy post- transplantation **[14]**.

This retrospective study was planned to find the value of MELD score to predict the response and complications after DAAs therapy in "difficult to treat" chronic HCV patients.

MELD score improved in 28.6% of patients worsened in 14.3% and remain stable in 57.1%. Deterding et al. studied 80 patients with advanced HCV associated liver cirrhosis of genotypes 1, 2, 3 and 4 receiving different combinations of DAAs. MELD scores improved until post-treatment week 12 in 44% of the patients, remained stable in 41%and worsened in 15% and CPT scores improved in 25% of patients **[9]**. Foster et al. reported changes in MELD score 4 weeks after the cessation of DAAs therapy in advanced HCV-associated liver cirrhosis patients where 47.7% had no significant change, 41.8% improved by ≥2 points; and 10.5% worsened by ≥2 points **[10]**. In another retrospective, national, multi-center study in patients from the Spanish Hepa-C registry investigated the effectiveness and safety of all currently approved DAAs regimens in patients with advanced liver disease, including those with decompensated cirrhosis. Overall, 36% showed improvements in MELD score, 31% had no change and 33% worsened **[15]**. All these results are suggesting that eradication of the virus can improve hepatic function rapidly by attenuating the injury and inflammation caused by HCV replication.

In this study, before treatment, mean MELD score in patients who reported complications during treatment was significantly higher when compared with patients without complications indicating that the high MELD score is a predictor of occurrence of complication. However, because of the small number of patients with complications (n=5), the exact predictive cutoff value of MELD cannot be calculated by the specific statistical tests used for this purpose. A similar result was reported by Manns et al. who observed that the patients with baseline MELD score <15 reported more improvement of their MELD after treatment and rarely develop complications while those who had baseline MELD score ≥15 were in the opposite side **[16]**.

In this study, one patient was reported to develop hepatocellular carcinoma (HCC) after treatment. Although DAAs may improve liver function parameters in chronic HCV patients, HCC may still develop. It is well established that HCC can occur after interferon-induced SVR even if the relative HCC risk is reduced **[17]**. Deterding et al. observed five cases of HCC in 80 cirrhotic patients treated with DAAs and followed up for only 6–9 months highlighting the need for careful monitoring even if HCV RNA is negative **[9]**.

In this study, before treatment, mean MELD score in patients who achieved SVR didn't show significant difference when compared with patients who didn't achieve SVR indicating that MELD score cannot be used as a predictor of response to DAAs. This result can be explained by the significant decrease in the mean MELD score in patients with SVR and the unchanged score of patients without SVR after treatment. This result is not matching with that of Carrillo et al. 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). Carrillo and his colleague put Child B/C patients in one group leading to decreased response rate of this group. In addition, 67% of Child B patients in that study had score 7 which is the nearest score to Child A making those to achieve high SVR rate near to that of Child A **[15]**.

CONCLUSION

Baseline MELD score cannot predict the response to treatment of 'difficult to treat' chronic HCV patients but can predict the occurrence of complications.

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

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Conflicts of interest: None.

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