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RESEARCH ARTICLE

Pretreatment Factors Predicting Sustained Virological Response to Pegylated Interferon/Ribavirin Combination Therapy in Egyptian Patients with Hepatitis C Virus Genotype 4

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Abstract

Background: Hepatitis C virus (HCV) is a growing health problem worldwide. Egypt has the highest HCV prevalence in the world. In the last decade, HCV-related morbidity doubled, and HCC related to HCV increased almost threefold. The desired goal with combination antiviral therapy is to obtain a sustained virologic response (SVR). The predictors of SVR of genotype-4 are not well represented because most of the data were on genotype-1; therefore, there is a need for further studies. **Aim:** To clarify the predictors of SVR to combination therapy in patients with HCV infection genotype-4 before initiating treatment. **Patients and Methods:** This retrospective study included 530 HCV patients treated with combination therapy pegylated interferon plus ribavirin. The patients were divided into two groups: SVR patients (Group I) and Non-SVR patients (Group II). **Results:** A significantly higher age was found in group II when compared with group I (P=0.0008). Also, a significantly higher pretreatment ALT, AST, alkaline phosphatase and HCV-RNA viral load levels were found in group II when compared with group I (P< 0.0001) for all. Patients with (age >40 years, pretreatment ALT level >2 folds, bilharziasis history, late fibrosis stages and late activity stages) were prone to be non-SVR than the others. **Conclusion:** Patients with (age >40 years, pretreatment ALT level >2 folds, bilharziasis history, late fibrosis stages and late activity stages) were prone to be non-SVR than the others. These findings may have important prognostic, cost saving and therapeutic implications in HCV patients treatment.

INTRODUCTION

Hepatitis C virus (HCV) is a major health problem worldwide. Approximately 3% of the world's population (130–170 million) is chronically infected with HCV [1,2]. Egypt has the highest HCV prevalence in the world [3]. In the last decade, HCV-related morbidity doubled, and HCC related to HCV increased almost threefold [4]. Its impact on liver-related morbidity and mortality is expected to reach its peak in the next decade [5].

The desired goal with antiviral therapy is to obtain a sustained virologic response (SVR). In the last decade, treatment with pegylated interferon (pegIFN) alpha 2a or 2b combined with weight-based ribavirin (RBV) for 48

weeks, has been considered the standard of care for HCV genotype 4 treatment, the most common genotype in Egypt [6].

SVR had been reported in more than 50% of patients treated with combination therapy using pegylated interferon α-2a or α-2b plus ribavirin [7]. The accurate prediction of HCV antiviral therapy response is of great interest. Host and viral factors, such as age, body weight, HCV genotype, baseline viral load and fibrosis stage may influence the response to therapy and can help physicians to predict treatment outcomes [8].

The predictors of response to genotype-4 are not well represented in the large clinical trials due to most of the data were on genotype-1 [9]. This gap has been largely filled by clinical trials from Saudi Arabia, Egypt, and Kuwait, where genotype-4 is predominant [10-12]. Data on predictors of response to therapy are limited and there is, therefore, a need for further studies. Thus, the aim of this study were to assess the predictors of SVR in patients with HCV infection genotype-4 before initiating treatment, as it is useful for patients and physicians to determine the likelihood of achieving SVR, so that they can decide whether treatment benefits outweigh its costs and risks.

Patients and Methods

Study Population

This retrospective study based upon data collection from medical records of previously treatment naïve 530 HCV patients with HCV infection treated with combination therapy pegylated interferon plus ribavirin. The patients were divided into two groups: SVR patients (Group I) and Non-SVR patients (Group II). All data files were collected from the Liver and Heart Institute in Kafr El-Sheikh, Egypt.

Coinfections with hepatitis B virus (HBV) and human immunodeficiency virus (HIV), active substance abuse, autoimmune hepatitis, hemochromatosis, α1-antitrypsin deficiency, Wilson's disease, hepatic decompensation and Patients with serum creatinine above 1.5 mg/dL, absolute neutrophil count (ANC) below 750/μL, platelet count below 100,000/μL, or hemoglobin below 10 g/dL at baseline were excluded from the study.

Treatment regimen

All patients initially were with active viral replication defined as detectable HCV-RNA and histology proved liver disease. The 530 patients with chronic HCV were treated either with pegylated interferon-alpha 2a (PEGASYS®, 180 μg per week) subcutaneous or with weight-based dosing of pegylated interferon-alpha 2b (PEG-INTRON®, 1.5 μg/kg per week) subcutaneous plus ribavirin orally (1000–1200 mg/day for body weight <75 or ≥75 kg, respectively) for 48 weeks according National Health Program. Treatment was stopped at week 12 if serum HCV-RNA was still detectable. To maintain the starting dose combination therapy, the patients were given erythropoietin and granulocyte-colony stimulating factor if they developed treatment-induced anemia (<10 g/ dL) or neutropenia (ANC below 750/μL), respectively.

SVR was defined as an undetectable HCV-RNA level 24 weeks after treatment withdrawal analyzed by sensitive polymerase chain reaction (PCR) as real time PCR. Patients with detectable serum HCV-RNA at weeks 12, 24, 48, and 72 of treatment were characterized as non-SVR patients.

Clinical and laboratory assessment

Patients' demographic and clinical data were obtained by a careful review of their hospital medical records. Each patient's age, gender, risk factors for contracting HCV infection, treatment side effects were documented on a data extraction sheet. All patients were clinically, hematologically, and biochemically evaluated before starting treatment and at weeks 12, 24, 48, and 72 of treatment follow-up or as needed.

Virologic assessment

Serum HCV-RNA levels were measured using automated extraction system (Cobas Amplicor) Abbott Real Time M2000 with a HCV-RNA detection rate range of 30–100,000,000 IU/mL. Serum HCV-RNA level was measured before starting treatment and at treatment weeks 12, 24, and 48, and 24 weeks after treatment end.

Liver histology

Liver biopsy was performed at baseline, by an 18-gauge Monopty liver biopsy needles (Bard Technologies, Covington, GA, USA). Necroinflammation and fibrosis were assessed using the Metavir score [13]. Patients who

declined to have a liver biopsy had the option of an alternative noninvasive liver fibrosis test, such as FiboTest-ActiTest® (Biopredictive, France).

Statistical analysis

The collected data was tabulated and analyzed using SPSS statistical package version 21.0, IBM corporation software group, USA. Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. Comparison of continuous data between two groups was made by using unpaired t-test for parametric data and Mann-Whitney test for nonparametric data. Fisher's exact and Chi square test were used for comparison between Categorical data. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

RESULTS

This study included 2 groups: **Group I (SVR):** 246 chronic HCV patients (146 male & 100 female) with SVR; their ages ranged from 20 to 58 years (mean 37.78±9.674). **Group II (Non-SVR):** 284 chronic HCV patients (152 male & 132 female) without SVR; their ages ranged from 20 to 59 years (mean 40.61 ±9.506).

In the present study, a significantly higher age was found in group II when compared with group I (P=0.0008). Also, a significantly higher pretreatment ALT & AST were found in group II (mean 63.97 ± 26.074 U/L) (mean 57.59 ± 23.628 U/L) when compared with group I (mean 52.15 ± 26.104 U/L) (mean 49.38± 23.628 U/L) with (P< 0.0001) and (P< 0.0001) respectively. Our results also showed, a significantly higher pretreatment alkaline phosphatase was found in group II (mean 129.06 ± 40.088 U/L) when compared with group I (mean 103.86 ± 31.156 U/L) (P< 0.0001) and a significantly higher pretreatment HCV-RNA viral load was found in group II (mean 11.38 ± 21.804 $x10^5$ copies/ml) when compared with group I (mean 6.45 ± 13.779 $x10^5$ copies/ml) (P< 0.0001). **(Table 1)**

Our study showed that patients with (age >40 years, ALT level >2 folds, bilharziasis history, late fibrosis stages and late activity stages) were prone to be non-SVR than the others. **(Table 2) (Figures 1, 2, 3)**

Table (1): Quantitative demographic and pretreatment investigatory data of the 2 studied groups.

Variables	Group I (SVR) Mean ± SD	Group II (Non-SVR) Mean ± SD	p
Age (years)	37.78 ± 9.674	40.61 ± 9.506	**0.0008***
Body mass index (BMI) (Kg/m^2)	26± 2.453	25.77 ± 2.556	0.3730
Alanine aminotransferase (ALT) (U/L)	52.15 ± 26.104	63.97 ± 26.074	**<0.0001***
Aspartate aminotransferase (AST) (U/L)	49.38± 23.198	57.59 ± 23.628	**<0.0001***
Alkaline phosphatase (U/L)	103.86± 31.156	129.06 ± 40.088	**<0.0001***
Total bilirubin (mg/dl)	0.90 ± 0.1989	0.91 ± 0.1855	0.5656
Serum Albumin (g/dl)	4.46 ± 0.3728	4.42 ± 0.3656	0.1200
Prothrombin concentration (%)	90.01 ± 8.479	89.35 ± 7.481	0.0972
Fasting plasma glucose (mg/dl)	97 ± 16.575	98.76 ± 30.384	00743
Serum creatinine (mg/dl)	0.84 ± 0.1615	0.84 ± 0.1729	0.8784
thyroid-stimulating hormone (TSH) (uIU/ml)	1.67 ± 0.8338	1.64 ± 1.000	0.3405
Hemoglobin (g/dl)	13.78 ± 1.509	13.71 ± 1.333	0.5320
White blood cells (WBCs) $x10^9$/L	6.34 ± 1.942	6.27 ± 1.755	0.9467
Platelets $x10^9$/L	210.89 ± 58.94	203.86 ± 58.709	0.1385
HCV-RNA viral load ($x10^5$ copies/ml)	6.45 ± 13.779	11.38 ± 21.804	**<0.0001***

Table (2): Categorical demographic and pretreatment investigatory data of the 2 studied groups.

Variables		Group I (SVR) (N=246) (number)(%)	Group II (Non-SVR) (N=284) (number)(%)	P
Sex	**Male**	146(59.35%)	152(53.52%)	0.1886
	Female	100(40.65%)	132(46.48%)	
Age	**≤ 40 years**	147(59.76%)	127(44.72%)	**0.0007***
	> 40 years	99(40.24%)	157(55.28%)	
Body mass index	**<25 Kg/m^2**	79(32.11%)	92(32.39%)	1.000
	≥ 25 Kg/m^2	167(67.89%)	192(67.61%)	
Alanine aminotransferase	**≤ 2 folds**	214(86.99%)	227(79.93%)	**0.0357***
	> 2 folds	32(13.01%)	57(20.07%)	
Aspartate aminotransferase	**≤ 2 folds**	206(83.74%)	219(77.11%)	0.0633
	> 2 folds	40(16.26%)	65(22.89%)	
Diabetes mellitus	**+ve**	10(4.07%)	14(4.93%)	0.6801
	-ve	236(95.93%)	270(95.07%)	
Smoking	**+ve**	36(14.63%)	45(15.85%)	0.7182
	-ve	210(85.37%)	239(84.15%)	
Interferon type	**Peg INF-α2a**	164(66.67%)	178(62.68%)	0.3632
	Peg INF-α 2b	82(33.33%)	106(37.32%)	
Ribavirin dose	**1000 mg/day**	111(45.12%)	118(41.55%)	0.4294
	1200 mg/day	135(54.88%)	166(58.45%)	
Bilharziasis history	**+ve**	94(38.21%)	201(70.77%)	**<0.0001***
	-ve	152(61.79%)	83(29.23%)	
Fibrosis	**F0**	23(9.35%)	Zero (0%)	**<0.0001***
	F1	134(54.47%)	115(40.49%)	
	F2	78(31.71%)	137(48.24%)	
	F3	11(4.47%)	32(11.27%)	
Activity	**A0**	12(4.88%)	1(0.35%)	**0.0006***
	A1	197(80.08%)	179(63.03%)	
	A2	35(14.23%)	96(33.80%)	
	A3	2(0.81%)	8(2.82%)	

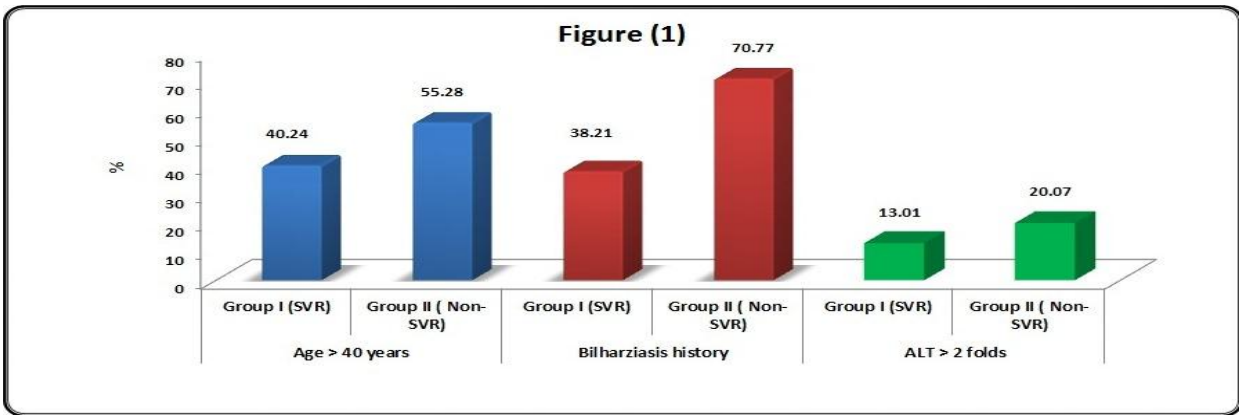

Figure (1): Age over 40 years,* bilharziasis history and ALT > 2 folds *percentages in the studied groups.

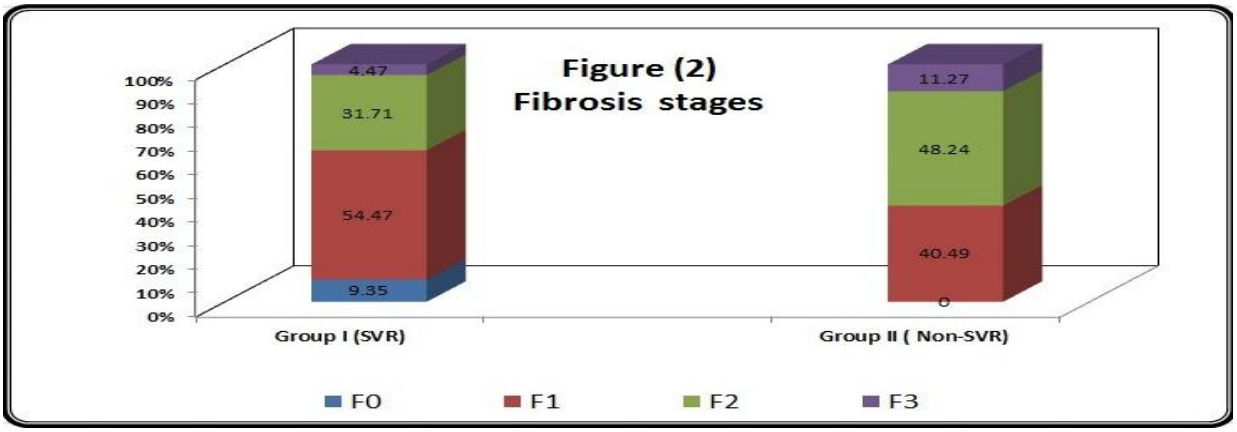

Figure (2): Fibrosis stages percentages in the studied groups.

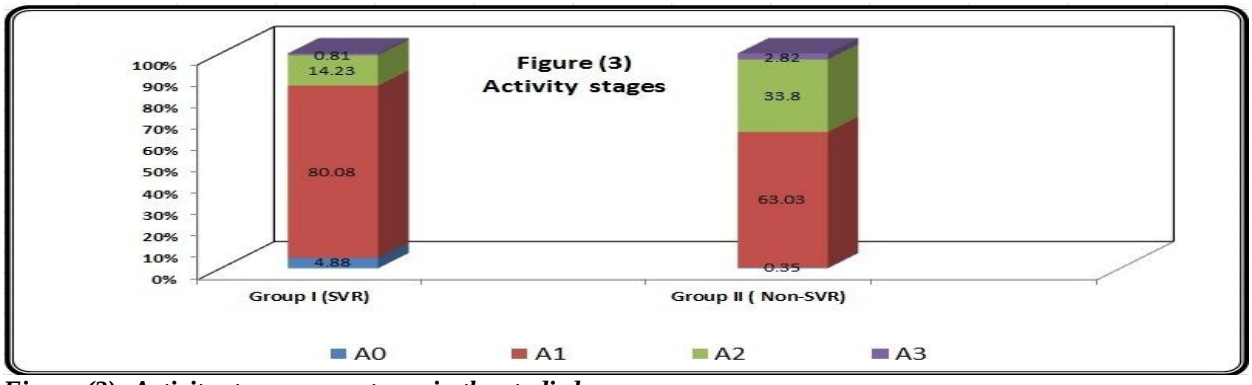

Figure (3): Activity stages percentages in the studied groups.

Discussion

As long as the treatment of (HCV) infection is expensive and is associated with many side effects, patients and physicians will need to know the likelihood of the response, so that they can decide whether the benefits outweigh the risks and cost. The factors that determine this likelihood are called pretreatment predictors of response, and they can be classified as viral or host factors [14].

In the present study, a significantly higher age was found in group II when compared with group I (P=0.0008). Also, a significantly higher pretreatment ALT, AST, alkaline phosphatase and HCV-RNA viral load levels were found in group II when compared with group I (P< 0.0001) for all. On the other hand, insignificant differences between group I and group II as regard other demographic and investigatory parameters.

Our study showed that patients with (age >40 years, pretreatment ALT level >2 folds, bilharziasis history, late fibrosis stages and late activity stages) were prone to be non-SVR than the others.

In the same direction with our study, **Kau A et al., 2008** [15] showed that patients treated with pegIFN/RBV combined therapy with younger age significantly correlated with the likelihood of obtaining SVR. Furthermore, higher SVR rates were obtained in patients younger than 40–45 years old [15] . Moreover, in older age there are more imbalances of cellular, humoral, and innate immunity, therefore the aged patients are more likely to have more advanced liver diseases [16].

Hsu CS et al., 2009 [17,] **Ismail MH, 2013** [18] and **El Khateeb AA et al., 2014** [19] showed insignificant difference between patients with SVR and patients without SVR as regard sex.

In agreement of our results, **Hsu CS et al., 2009** [17] and **El Khateeb AA et al., 2014** [19] showed insignificant difference between patients with SVR and patients without SVR as regard BMI. Also, **Ismail MH, 2013** [18] proved that obesity was not confirmed as independent baseline predictor to SVR.

Also, **Hsu CS et al., 2009** [17] showed insignificant differences between patients with SVR and patients without SVR as regard total bilirubin, serum albumin, fasting blood glucose, white blood count, hemoglobin level, and platelet count. **El Khateeb AA et al., 2014** [19] showed that the pretreatment hemoglobin, platelets and white blood cells didn't show any significant difference between patients with SVR and patients without SVR.

In agreement of our results, **Kau A et al., 2008** [15] proved that patients with chronic HCV infection having advanced fibrosis, especially cirrhosis, is associated with a diminished treatment response. Also, **Gad RR *et al.*, 2008** [12] reported that patients with severe fibrosis (F > 2) were half as likely to achieve SVR compared with those with mild fibrosis. **Hsu CS et al., 2009** [17] **and El Khateeb AA et al., 2014** [19] showed significant difference between patients with SVR and patients without SVR as regard fibrosis stages.

On the same direction of our results some authors proved that HCV RNA levels before initiating treatment predict the likelihood of obtaining SVR with pegIFN/RBV combined therapy [20,21]. **Zeuzem S et al., 2004** [22]**, Kamal SM et al., 2007** [11]**, Al Ashgar H et al., 2009** [23]**, and Ismail MH, 2013** [18] identified low viral load as independent positive predictor of an SVR. **Backus LI *et al*.,2007** [24] identified 5944 hepatitis C patients who were treated at Veterans Affairs Health Care with PEG-INF/ribavirin and found that patients with low viremia (500,000 IU/mL) were more likely to respond than patients with a high viral load . **Hsu CS et al., 2009** [17] showed significant difference between patients with SVR and patients without SVR regarding HCV RNA levels.

In the opposite side to our results, **Hsu CS et al., 2009** [17]**, Ismail MH, 2013** [18] **and El Khateeb AA et al., 2014** [19] showed insignificant difference between patients with SVR and patients without SVR as regard age. **Poynard T et al., 1998** [25] showed that there were significant differences in SVR rate with the female. Female sex is positively associated with SVR.

In the opposite side to our study, **Hsu CS et al., 2009** [17] showed insignificant differences between patients with SVR and patients without SVR as regard ALT, AST and activity stages. Also, **El Khateeb AA et al., 2014** [19] showed that the patients with SVR and non-SVR did not differ in the pretreatment levels of ALT, AST, alkaline phosphatase, and degree of viremia.

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In our study, History of bilharziasis was considered as a predictor of treatment non response. In the opposite side, **Derbala MF et al., 2006** [26] showed that bilharziasis didn't affect the response for treatment. Bilharzial infestation predominates in Egypt, so it must be considered in pretreatment assessment for HCV patients. HCV patients co-infected with bilharziasis have increased incidence of viral persistence with high HCV-RNA titers and accelerated fibrosis. This may be due to the fact that bilharziasis have a down regulated immune response to HCV in the form of reduced IFN-γ, interlukin-4 (IL-4) and IL-10 secreted by HCV-specific T cells [27].

Conclusions

Results from this study can be concluded as: Patients with (age >40 years, pretreatment ALT level >2 folds, bilharziasis history, late fibrosis stages and late activity stages) were prone to be non-SVR than the others. These findings may have important prognostic and therapeutic implications.
We recommend large scale multicenter studies covering the different Egyptian population to better clarify the factors predicting SVR to pegylated interferon/ribavirin combination therapy in Egyptian patients with HCV genotype 4 even with the new use of directly acting antiviral agents (DAAs) as sofosbuvir.

Authors' contributions:

Conception, design and Supervision of all field activities: Tamer A. Elbedewy, Hadier M. Fouad, Fotouh R. Mansour.

Collection and assembly of data: Hadier M. Fouad, Fotouh R. Mansour, Ahmed D. Khalifah, Ahmed A. Ibrahim, Soad S. Mandouh, Yomna M. El-gazar, Gehad S. Ahmedy, Samya k. El-shenawy, Eman E. Badr, Gehad A. Gad, Tasneem S. Abo El-fadl, Aya S. El-gazar, Samar S. kasem, Mona A. Abd ELgliel, Alaa G. Amin, Wesam T. Hamamsy, Alaa S. Othman, Sherin H. Mostafa, Tagreed G. Anwar, Hossam M. Gadallah.

Data analysis, data interpretation, Manuscript writing and made the final critical revision of the manuscript for important intellectual content: Tamer A. Elbedewy.

All authors approved the final version of the manuscript.

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Competing interests:

All the authors declare that they have no competing interests.

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