Predictors of HCV Response to Treatment with Pegylated Interferon and Ribavirin in Sharkia Governorate

A retrospective study among patients involved in the National Campaign for Treatment of Chronic Hepatitis C in Sharkia Governorate in Egypt

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Background and study aim: The current standard of care (SOC) for chronic hepatitis C (CHC) in Egypt is pegylated interferon and ribavirin (PEG-INF/RBV) for 48 weeks, which is expensive, can be difficult to tolerate and with high failure rate. Additional information about predicting sustained virologic response (SVR) may be helpful in making proper decisions of treatment. This is a retrospective observational cohort study which was designed to identify predictors of SVR to PEG-INF/RBV among a cohort of Sharkian patients in Egypt

Patients and methods: 2991 patients with CHC fulfilling all inclusion and exclusion criteria for treatment were enrolled in this study. Patients were allocated randomly to treatment with either PEG-INF α2a/RBV (67.8%) or PEG-INF α2b/RBV (32.2%). Virologic monitoring was planned to be tested basically and at weeks 12, 24, 48 and 72 weeks after initiation of treatment.

Results: Analysis of data could be applied to 795 (26.6%) patients of the cohort because of their adherence to protocol and availability of treatment and follow up data. The remaining participants of the study (73.4%) were excluded because of lack of essential data and drop out for various reasons. Overall SVR was encountered in 404 (50.8%) patients and in 54.9% and 44.2% for patients treated with PEG-INF α2a and PEG-INF α2b respectively (p< 0.0001). Responders had statistically significant lower levels of fasting blood sugar, ALT, AST, indirect bilirubin, α fetoprotein, hemoglobin, stage of liver fibrosis and HCV RNA and higher values of alkaline phosphatase,serum albumin, prothrombin time , absolute neutrophil and platelet counts. In multivariate linear regression analysis, early virologic response (EVR) and receiving PEG-INF α2a (rather than PEG-INF α2b) were predictors of SVR.

Conclusion: Overall SVR among Sharkian patients with CHC, treated with SOC therapy is 50.8%. EVR is the best independent predictor of SVR. The form of PEG-INF may also predict the treatment response. None of the initial pretreatment variables could predict the SVR to treatment with the current SOC for CHC.

INTRODUCTION

Hepatitis C Virus (HCV) infection is a global health problem with worldwide prevalence of about 3% [1, 2]. The highest prevalence of infection in the world is recorded in Egypt. According to Egypt Demographic Health Survey (EDHS) published in 2009, 14.7% of Egyptians between 15 and 59 years old are positive for HCV antibodies and 9.8% have active infection with positive HCV RNA viremia [3]. This report of EDHS provides a precise national prevalence estimate and includes additional data on patterns of HCV prevalence by gender, age, urban vs. rural, and between different regions of the country. Age was the strongest and most consistently associated factor to HCV prevalence and HCV RNA positivity.

In Sharkia Governorate the prevalence of HCV infection is estimated to range from 4.8% among people < 20

years old to 41.9% among people > 40 years old, with an average prevalence of 25.8%[4]. The significant predictors of HCV infection, according to the same group of investigators, were previous parenteral therapy for Schistosomiasis among people more than 20 years old, blood transfusion, invasive procedures (surgery and endoscopy) and use of contaminated syringes as well as shaving at community barbers [4].

Validated mathematical models for estimating incidence from age-specific prevalence of HCV infection among Egyptians were used. The modeled incidence from the national study and collectively from the modeled incidence from the previous community studies was 6.9/1,000 [95% confidence interval (CI), 5.5–7.4] per person per year and 6.6/1,000 (95% CI, 5.1–7.0) per person per year, respectively. Projected to the age structure of the Egyptian population, more than 500,000 new HCV infections per year were estimated [5].

There are 6 major genotypes of HCV [6] and more than 50 subtypes [7, 8]. About 91% of the Egyptian patients are infected with genotype 4 [9]. Each genotype differs from the others by 30%-35% of its nucleotide site sequence and also exists as numerous genetically distinct isolates [6,10].

Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy. Thus, each genotype can be considered a phylogenetically distinct entity requiring its own specific clinical appreciation. Knowledge of the epidemiology of HCV genotypes is essential not only for epidemiological reasons but also from a clinical standpoint. The infecting HCV strain is known to be one of the main independent factors that influence the outcome of antiviral therapy [7, 10]. Genotypes 1, 2, and 3 are common throughout the United States and Europe [7, 11] and have thus become the focus of much interest and research. The clinical presentation and management of infections arising from these viral genotypes has advanced rapidly. In contrast, genotype 4, which is prevalent in Egypt, has not been adequately studied; therefore, the management strategies for patients infected with this genotype are not as well developed .

The major problem of HCV infection, regarding its natural history, is the high rate of chronicity after viral infection. More than 80% of infected patients become chronic [12]. Chronic HCV infection leads to liver cirrhosis in 10-20% of cases within 20 years, with some studies showing estimates up to 50% [13, 14, 15, 16]. About 5% of HCV cirrhotic patients are at risk of decompensation every year [14]. Hepatocellular carcinoma is common in HCV patients with cirrhosis, with an estimated risk of up to 3% per year [17, 18].

The current standard of HCV therapy in Egypt is based on combination of pegylated interferon and ribavirin for 48 weeks. There are 3 kinds of pegylated interferon in the Egyptian market; Pegasys (Pegylated interferon α2a with 40 KD side chain) by Roche, PEG-Intron (Pegylated interferon α2b with 12 KD side chain) by Schering and Reiferon Retard (Pegylated interferon α2a with 20 KD side chain) by Minapharm.

Sustained virological response (SVR), defined as undetection of HCV RNA in patient's serum for 6 months after end of treatment, is ranging from 42.9% to 69% [19-28] in patients with genotype 4. This means that between 31-57% of patients fail to respond to the current therapy. This failure of response is likely because of a combination of viral and host factors.

Several studies, including pivotal trials, assessed baseline host and viral predictors such as body weight, ethnicity, liver histology, genotype, and viral load [29, 30]. In order of descent, viral load, ethnicity, fibrosis, steatosis, diabetes mellitus, and alanine aminotransferase (ALT) were found to have significant impact on sustained virological response in a multivariate regression analysis [31]. Viral load remains the most important single variable prior to therapy, but one that cannot be altered. Other variables, however, may be modified prior to treatment. It is clear that metabolic factors such as elevated fasting glucose and the histologic finding of steatosis are important negative predictors [32].

Considering the high failure rate of response in addition to the very high cost and significant side effects of the current treatment, predicting the possibility of response to treatment prior to initiating therapy would be very useful.

We hypothesize that identification of validated pretreatment predictors of response and failure among our unique patients would help in forwarding our national guidelines of HCV

treatment for better clinical outcomes and more favorable economic impact.

The objective of this study is to find out what are the reliable baseline predictors of treatment response unique to Egyptian patients with chronic hepatitis C infection. Another objective is to identify the SVR rate among our patients.

PATIENTS AND METHODS

This is a retrospective observational study analyzing data of patients selected for SOC therapy for CHC in "Al-Ahrar Center for Treatment of Hepatitis C Infection". This center is located in Zagazig City, the capital of Sharkia Governorate, one of the Eastern Delta Governorates of Egypt. This center, and many others all over Egypt, was established in February 2008 by the "National Committee for Treatment of Viral Hepatitis". Patients were enrolled in the study from March 12, 2008 to June 3, 2009 with follow up to November 4, 2010. All patients were treated under full sponsorship by Ministry of Health.

Patients were selected according to the inclusion and exclusion criteria of the national protocol for the treatment of CHC and were subjected to: thorough history taking, complete clinical examination and undergone the pre-enrollment investigations in the form of fasting blood glucose level and HbA1C for diabetic patients, serum creatinine, serum albumin, AST and ALT serum level, serum alkaline phosphatase level, total & direct bilirubin levels, hemoglobin concentration, WBC's count and platelets count, prothrombin time , INR , PTT , PC, pregnancy test for female patients, hepatitis B surface antigen, anti HCV antibody, quantitative HCV RNA (PCR) assay, serum α-fetoprotein level, ANA titer, TSH level, pelvi-abdominal ultrasonography, ECG for male patient over 40 years, female patient over 50 years, Ocular and fundus examination, Anti-schistozomal antibody and liver biopsy with histopathological examination using Metavir Scoring System for assessment of stage of fibrosis and grade of inflammatory activity.

All patients must fulfill all the Inclusion criteria which are: male or female patient aged 18 - 60 y, Hb ≥ 12 g/dl (for males) and 11 g/dl (for females), WBC's count ≥ 3,500/µL , neutrophil's count ≥ 1,500/µL and platelet's count≥ 85,000/ /µL, Prothrombin time not more than 3 sec. above the control value, direct bilirubin ≤ 0.4mg/dl or within 20% of ULN, indirect bilirubin ≤ 1 mg/dl or within 20% of ULN, fasting blood glucose ≤ 115 mg /dl or HbA1c < 8.5 for diabetics, serum albumin ≥ 3.5 g/dl, serum creatinine < 1.5 mg/dl, negative hepatitis B surface antigen, negative ANA or less than 1/160, positive anti- HCV antibody, positive HCV– RNA , serum α-fetoprotein less than 100 ng/ml , proper contraceptive methods for both partners(double contraception) and a written informed consent.

Exclusion criteria of the treatment program include : patients with any other cause of liver disease (Hepatitis B, hemochromatosis, Wilson's disease), alcoholic liver disease, fatty liver disease, decompensated liver disease, hypersensitivity to interferon or ribavirin, autoimmune liver or systemic diseases, pregnant or breast feeding female, clinically significant retinal disease, acute coronary syndrome in the last 6 months, drugs related liver disease, patients with CNS trauma that require medical treatment and patients with active seizures.

Candidate patients were allocated randomly for treatment with one of two regimens: (1) Pegylated interferon α2a (180 µg s.c once weekly) plus ribavirin (1000-1200 mg p.o daily for patients with body weight < 75 or ≥ 75 kg respectively). (2) Pegylated interferon α2b (1.5 µg s.c once weekly) plus ribavirin (800-1400 mg p.o daily according to body weight as recommended by the manufacturer).

The protocol for follow up of treated patients included regular clinical evaluation with inquiry about any side effects and laboratory estimation of CBC, ALT, AST, Total bilirubin, serum creatinine at week 1, week 2 , week 4 and every 4 weeks thereafter up to week 48. HCV RNA was tested at weeks 12, 24, 48 and 72 after initiation of treatment. The patient was considered responding and continued treatment if the 12 week HCV RNA was undetected (complete early virologic response) or reduced to less than 1% of pretreatment levels (partial early virologic response). If the HCV RNA didn't drop to less than 1% of baseline level at week 12 or was detected qualitatively at week 24 the patient was considered not responding and his treatment was stopped at that point. SVR was achieved if HCV RNA became undetected at week 24 and remained so up to week 72 of follow up.

STATISTICAL ANALYSIS

Data were checked, entered and analyzed using software computer package (SPSS version 17) for interpretation of the results. Data expressed as number and percentage for qualitative variables and as mean ± standard deviation for quantitative variables. Significance was used as appropriate and P less than 0.05 was considered statistically significant. The t-test for independent samples was used to compare variables of two groups. Chi square was used to compare proportions. Multivariate linear regression analysis was used to identify independent predictors of SVR.

RESULTS

We identified 2991 patients who started treatment with PEG-INF/RBV (fig.1). 2196 (73.4) patients were excluded (drop out) because of many reasons: 1) transfer to other centers (for geographical reasons), 2) intolerability of medications, 3) discontinuation of treatment because of occurrence of serious side effects, 4) loss of follow up mostly with lack of HCV RNA results at end of treatment or at week 72, 5) missing essential data that interfere with proper analysis.

Only 795 (26.6%) subjects of the cohort were available with complete data (basic and follow up) for protocol statistical analysis.

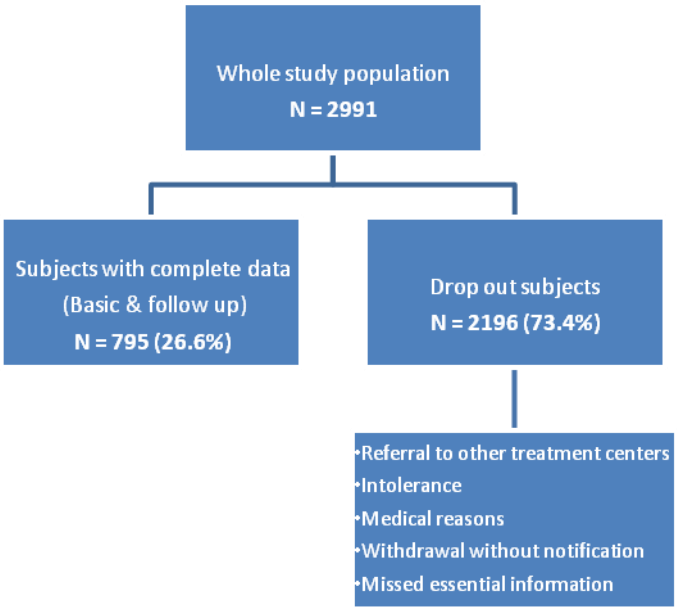

Figure (1): A chart showing subjects enrolled in the study with intension to treat (ITT)

The chart in fig.2 shows the response of these patients to treatment. EVR {defined as ≥ 2 log reduction (pEVR) or undetection of HCV RNA (cEVR) after 12 weeks of therapy} was encountered in 666 (83.8%) patients. 585 (73.6%) and 81 (10.2%) patients achieved cEVR and pEVR respectively.

ETR (defined as undetection of HCV RNA after 48 weeks of therapy was identified in 484 (60.9%) patients. SVR (defined as undetection of HCV RNA 24 weeks after end of treatment was identified in 404 (50.8%) patients as per protocol analysis. Considering the initial number of patients enrolled in the study with intention to treat (ITT), this percentage of patients with SVR drops to 13.5% which raises a questionable conclusion in front of the health policy-makers in Egypt.

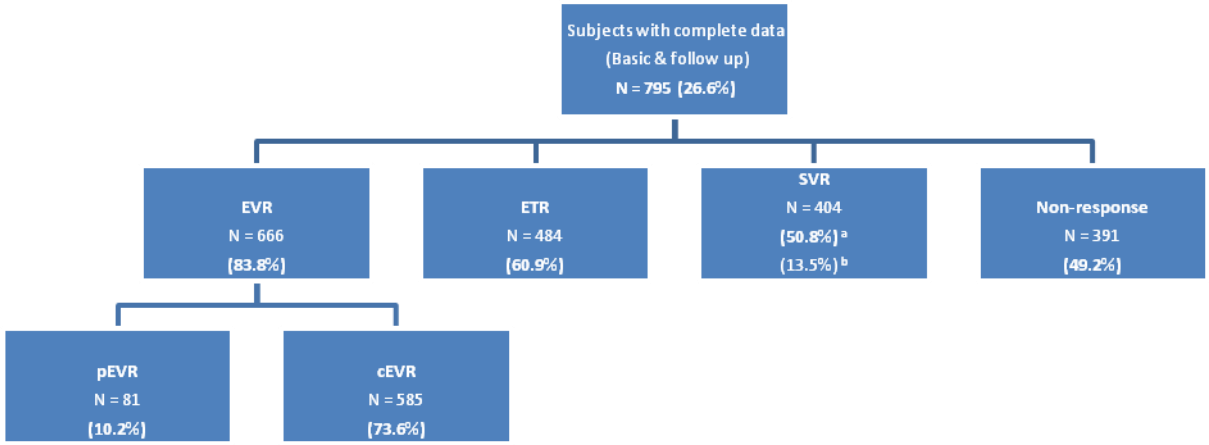

Figure (2) A chart showing Virologic Response to Treatment (EVR = early virologic response, ETR = end of treatment response, SVR = sustained virologic response, pEVR = partial virologic response, cEVR = complete early virologic response). **a:** Per protocol analysis **b:** per ITT analysis

The chart in fig.3 shows the response to treatment with different types of PEG-INF in our protocol. SVR was encountered in 54.8% and 43.9% in patients treated with PEG-INF α2a and PEG-INF α2b respectively (χ^2=24.144, p<0.0001).

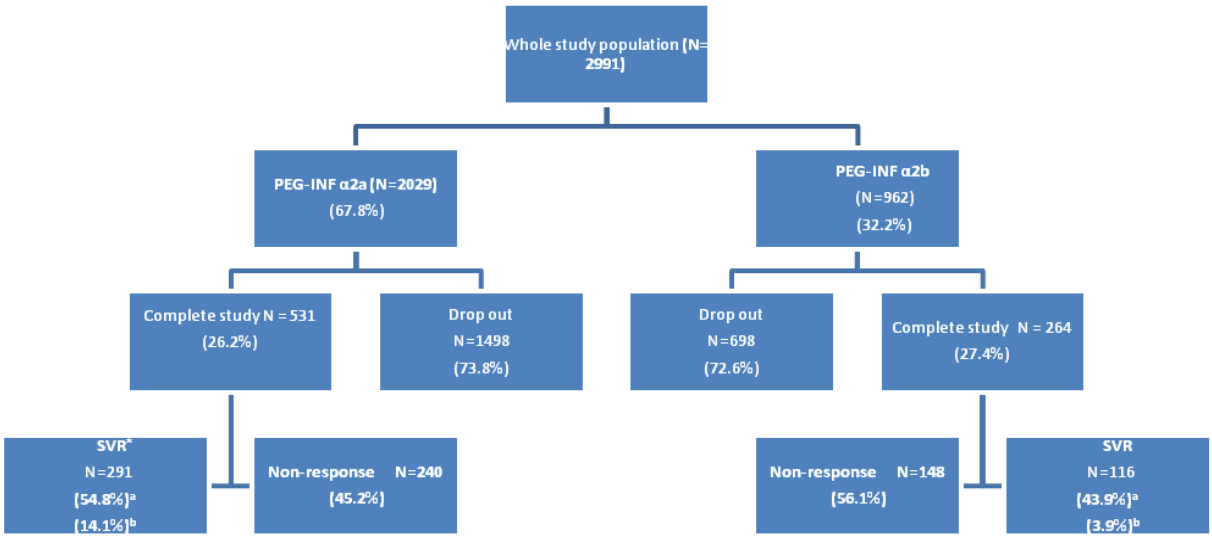

Figure (3) A chart showing Virologic Response to Treatment with PEG-INF α2a & PEG-INF α2b (a: Per protocol analysis **b:** per ITT analysis)
* p<0.0001 (χ^2 =24.144) compared with SVR in PEG-INF α2b arm

Table (1) shows the baseline characteristics of study population. 795 patients were included with average age 41.7 ± 8.8 years, 617 (77.6%) patients were males with average body weight 83±12.4 kg and BMI 30.3±3.86 kg/m^2.

Table (2) compares the mean ± SD of various data between responders and non-responders to treatment with PEG-INF/RBV. Responders were significantly characterized by having more percentage of males, lower levels of FBS, ALT, AST, Indirect bilirubin, serum albumin, α fetoprotein and hemoglobin, but higher levels of serum ALKP, PT, ANC and platelet count. Responders were also characterized by having

milder degrees of liver fibrosis and lower baseline values of serum HCV RNA. There was no statistically significant difference between responders and non-responders regarding age, body weight or BMI.

Table (3) compares the mean ± SD of various baseline data and SVR between patients treated with PEG-INF α2a and PEG-INF α2b. The percentage of males was significantly higher in patients treated with PEG-INF α2a, while the degree of inflammatory activity was milder in patients treated with PEG-INF α2b. Regarding other baseline variables, there was no statistically significant difference between both groups.

SVR was encountered in 54.9% and 44.2% of patients treated with PEG-INF α2a and PEG-INF α2b respectively (χ^2 =24.144, p<0.0001).

Using multivariate linear regression analysis (table 4), EVR was the best independent predictor of SVR (B±SE=0.67±0.118، 95% C.I =0.436 - 0.903, p 0000) followed by PEG-INF α2a (rather than PEG-INF α2b) (B±SE=0.378±0.108، 95% C.I =0.163 - 0.593, p 0.001).

Table (1): Baseline clinical, biochemical, histopathological and virological characteristics of the study subjects

Parameters	Minimum	Maximum	Mean	Std. Deviation (SD)
Age (years)	18	60	41.7	8.84
Weight (kg)	39	129	83	12.4
Height (cm)	141	190	173	9.11
BMI (kg/m^2)	22.22	39.4	30.3	3.86
Ribavirin (mg)	800	1400	1095.6	139.1
FBS (mg/dl)	55	346	97.1	29.7
Creatinine (mg/dl)	0.3	1.5	0.79	0.17
Albumin (g/dl)	3.5	5.3	4.1	0.44
ALKP (U/L)	11	310	113	43.42
AST (U/L)	2	272	40.9	37.39
ALT (U/L)	4	317	43.0	41.14
T.bilirubin (mg/dl)	0.1	1.5	0.84	0.25
I. bilirubin (mg/dl)	0.01	1	0.4	0.26
WBC ((/µL)	3500	17200	6772	2081
Hb (g/dl)	11	19.8	14.2	1.57
Plt. (/µL)	75000	770000	199850	65574
ANC (/µL)	1500	12300	3750.3	1591.2
PT (Seconds)	9.9	17	12.6	1.23
TSH (mU/L)	.03	17	1.85	1.26
HCV RNA (IU/ml)	97	47600000	534792	213287
AFP (ng/ml)	0.50	85	5.85	9.44
Fibrosis (Fo-4)	0.00	4	2.03	1.04
Activity (A0-3)	0.00	3	1.81	0.79

(BMI = body mass index, FBS = fasting blood sugar, ALKP = alkaline phosphatase, AST = aspartate aminotransferase, ALT = alanine aminotransferase, T.bilirubin = total bilirubin, I.bilirubin = indirect bilirubin, WBC = white blood cells, Hb = hemoglobin, Plt = platelets, ANC = absolute neutrophil count, PT = prothrombin time, TSH = thyroid stimulating hormone, AFP = alpha fetoprotein)

Table (2): Comparison of the mean ± SD of various clinical, biochemical and pathological parameters of the study

Parameters	**Responders (n=404)**	**Non-responders (n=391)**	t	P value
Age (y)	41.2± 8.8	42.1± 8.9	1.44	0.151
Sex M/F n (%)	325/79 (80.4/19.6)	292/99 (74.7/25.3)	X^2= 7.05	0.0079
Body weight(KG)	83.12 ± 12.5	82.9 ± 12.3	0.282	0.778
BMI (KG/m2)	30.2 ± 4.4	30.4 ± 3.5	0.129	0.898
FBS (mg/dl)	93.14 ± 21.7	101.3 ± 35.8	3.885	0.000
Serum creatinine (mg/dl)	0.79 ± 0.15	0.8 ± 0.18	0.913	0.361
Serum albumin (g/dl)	4.19 ± 0.42	4.08 ± 0.45	5.530	0.018
ALT (U/L)	35.9 ± 36.8	50.4 ± 44	4.987	0.000
AST (U/L)	31.4 ± 28.4	50.7 ± 42.8	7.468	0.000
Total Bilirubin (mg/dl)	0.82 ± 0.23	0.85 ± 0.27	1.765	0.078
Indirect Bilirubin (mg/dl)	0.41 ± 0.26	0.48 ± 0.27	2.886	0.006
ALKP (U/L)	117.6 ± 41.9	108.1 ± 44.5	3.028	0.003
Hb (g/dl)	14.09 ± 1.56	14.36 ± 1.58	2.432	0.015
WBC (/µL)	7023.4 ± 2206.6	6509.2 ± 1910.2	3.478	0.001
ANC (/µL)	3977.3 ± 1731.9	3483.8 ± 1368.5	2.404	0.017
Platelets (/µL)	207489 ± 58018	191871 ± 71845	3.349	0.001
AFP (ng/ml)	3.73 ± 4.79	8.12 ± 12.26	6.621	0.000
TSH (mU/L)	1.84 ± 1.136	1.85 ± 1.377	0.099	0.921
PT (seconds)	12.78 ± 1.19	12.48 ± 1.26	3.413	0.001
HCR RNA (IU/ml)	368961 ± 100002	707533 ± 286351	2.228	0.026
Fibrosis degree (F0-4)	1.94 ± 0.95	2.13 ± 1.11	2.453	0.014
Inflammatory activity (A0-3)	1.77 ± 0.79	1.84 ± 0.78	1.152	0.25
Ribavirin dosage (mg)	1091.8 ± 136.2	1099.7 ± 142.1	0.799	0.424

$P < 0.05$ was considered statistically significant.

Table (3): Comparison of the mean ± SD of various clinical, biochemical and pathological parameters of PEG-INF α2a -based therapy vs PEG-INF α2b -based therapy

Parameters	PEG-INF α2a (n=521)	PEG-INF α2b (n=260)	t	p
Age (Y)	42.1 ± 8.7	40.8 ± 8.9	1.92	0.055
Sex M/F (%)	398/122(76.5/23.5)	207/52 (80/20)	X= 3.89	0.049
Weight (Kg)	83.4±12.39	82 ± 12.46	1.53	0.125
BMI (Kg/m^2)	30.2±3.55	30.45 ± 4.57	0.197	0.844
Ribavirin (mg)	1096.5±136	1093.85 ± 145.33	0.255	0.799
FBS (mg/dl)	97.3±28.7	96.1 ± 29.8	0.55	0.582
Creatinine (mg/dl)	0.79±0.17	0.8 ± 0.16	1.009	0.313
Albumin (g/dl)	4.1±0.43	4.2 ± 0.45	1.832	0.067
ALKP (U/L)	114.15±42.66	111.41± 44.82	0.817	0.414
AST (U/L)	41.3±36.79	39.8 ± 38.78	0.531	0.595
ALT (U/L)	44.5±43.28	39.8 ±36.59	1.5	0.133
T. bilirubin (mg/dl)	0.845±0.26	0.82 ± 0.22	1.110	0.267
I. bilirubin (mg/dl)	0.46±0.27	0.42 ± 0.26	1.69	0.091
WBC (/uL)	6772±2011.9	6808 ± 2210.1	0.229	0.819
Hb (g/dl)	14.21±1.56	14.26 ± 1.6	0.442	0.658
Platelets (/uL)	200350.2±62424	199662.8±72048.7	0.137	0.891
ANC (/uL)	3747.8±1642.8	3757.3 ± 1455	0.041	0.967
PT (seconds)	12.68±1.21	12.55 ± 1.28	1.39	0.165
TSH (mU/L)	1.87±1.35	1.81 ± 1.07	0.571	0.568
RNA (IU/ml)	451824±104650	696031±339466	1.5	0.134
AFP (ng/ml)	6.2±10.53	5.1 ± 6.88	1.6	0.11
Fibrosis (F0-4)	2.02±1.03	2.04± 1.06	0.169	0.866
Activity (A0-3)	1.87±0.80	1.68 ± 0.74	3.07	0.002
SVR	54.9%	44.2%	χ^2 =24.144	<0.0001

P < 0.05 was considered statistically significant.

Table (4) Independent predictors of SVR in linear regression analysis

	B±SE	95% C.I	P
EVR	0.67±0.118	0.436 - 0.903	0.000
PEG-INF α2a	0.378±0.108	0.163 - 0.593	0.001

DISCUSSION

Although Baseline predictors are useful tools in assessing the relative difficulty of clearing hepatitis C virus (HCV), they have limited utility for selecting which patient should be considered for therapy and those patients with a reduced likelihood of successful therapy, perhaps sparing them the side effects and cost of therapy. Despite use of multiple variables, still there is no reliable way to ascribe an odds ratio for the chance that a particular patient will respond to therapy.

In chronic hepatitis C, the primary therapeutic goal is SVR, defined as undetectable HCV RNA by a sensitive assay at the end of a 24-week follow-up period after treatment completion. The current combination therapy consisting of pegylated (PEG) IFN plus ribavirin (RBV) for at least 48 weeks may be accompanied by numerous potentially dose-limiting side effects and SVR rates are still unsatisfactory with only approximately 50%[33,34] .

In the present study, responders were significantly characterized by having lower

levels of serum α fetoprotein. Moreover, there was a statistically significant difference between responders and non-responders regarding FBS. Many studies reported that diabetic patients achieved a lower SVR rate than that in nondiabetic subjects [35, 36]. It is clear that metabolic factors such as elevated fasting glucose and the histologic finding of steatosis are important negative predictors [32]. Moreover, higher baseline serum AFP levels predicted a lower SVR rate among patients with chronic hepatitis C [37]. However, we have shown that neither diabetes mellitus nor AFP levels were found to be independent predictors by multivariate regression analysis. These factors need to be assessed in HCV-4 patients in well-designed prospective studies.

Furthermore, responders were significantly having low ALT and AST [31]. A study by Zechini et al showed a statistically significant positive correlation of baseline aminotransferase values with the hepatitis activity index and fibrosis score, liver biopsies carried out in patients with normal transaminases show some degree of hepatic lesion, although, in most cases, histopathology of the lesion is mild and progression to fibrosis lower than in patients with elevated ALT [38].

A significant higher level of serum albumin, serum ALKP, PT, ANC (absolute neutrophil count) and platelet count were found in responder than in non-responder patients. However , further studies will be required to determine whether these findings bear any relationship to differences in rates of response to therapy among HCV patients.

In the present study, SVR was encountered in 50.8% of those who completed treatment. These results are similar to the responses achieved in previous studies that an anticipated SVR in genotype 4 patients is around 50% to 70% [39, 40]. Our study demonstrate a significant difference in SVR rates between pegylated interferon (PEG-IFN)- 2a plus ribavirin and PEG-INF α2b plus ribavirin respectively (e.g., 54.9% versus 44.2%; P = p<0.0001). However, the use of PEG-INF alfa-2 and RBV for 48 weeks lead to a substantial improvement in the rate of SVR [40)]

This study reported that a milder degrees of liver fibrosis predicted favorable response to treatment with pegylated interferon plus ribavirin in an analysis of participants [36, 40]. However, neither the fibrosis stage nor the inflammation grade in the pre-treatment liver biopsy was found to be independent predictor of SVR .

HCV viral load is one of the important factors to influence the response of antiviral therapy and considered as proxy determination of HCV replication [24, 41]. In this study responders were significantly characterized by having lower baseline values of serum HCV RNA. However HCV viral load was not found to be an independent predictor of SVR in our study. This is contrary to what was previously reported by other study [28].

In the present study, we found that EVR was the best independent predictor of SVR, so monitoring the early antiviral response to therapy can help identify those patients who are less likely to achieve SVR and therefore provide critical information for the overall management of patients with chronic hepatitis C [42, 43]. Also, we found that the type of interferon used in treatment was a contributor to the eventual outcome of therapy. Patients treated with pegylated interferon 2a were more likely to achieve viral clearance than those receiving the 2b form.

We can conclude that, the most reliable predictor of successful treatment is Early Virological Response, or EVR. If EVR is attained, treatment is continued, side effects and other factors permitting. If EVR is not attained, the patient is usually withdrawn from treatment, as the risk of taking the medication outweighs the predicted benefit of therapy. Form of PEG-INF may also predict the treatment response. None of the initial pretreatment variables could predict the SVR to treatment with the current SOC for CHC..

Funding: Non .

Conflicts of interest: Non .

Ethical Consideration: Signed informed consent is an integral part of this investigational and treatment protocol. The study was approved by the "National Committee for Treatment of Viral Hepatitis". We also got approval of the "Committee of Research Ethics of Faculty of Medicine, Zagazig University".

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