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Original Article

Hepatic fibrosis and serum alpha-fetoprotein (AFP) as predictors of response to HCV treatment and factors associated with serum AFP normalisation after treatment

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ABSTRACT

Background and study aim: Elevated levels of alpha-fetoprotein (AFP) can be seen in patients with chronic hepatitis C (CHC) and liver cirrhosis without hepatocellular carcinoma and were negatively associated with treatment response. However, factors associated with its changes are not identified. We aimed in this study to verify a cut-off value for AFP as a predictor of response to standard of care (SOC) antiviral therapy in Egyptian chronic hepatitis C virus (HCV)-infected patients and identify factors associated with its changes post treatment.

Patients and methods: A total of 175 chronic non-cirrhotic HCV-infected patients were evaluated for baseline serum AFP and liver biopsy were classified according to Ishak scoring system of hepatic fibrosis. All patients were scheduled to receive SOC antiviral therapy for 48 weeks and had been followed up to week 72. Reassessment of AFP and repeated liver biopsy at week 72 were feasible only in 79 patients.

Results: High baseline AFP levels were observed in non-respondents (non-sustained virological respondents (non-SVRs)) ($P < 0.01$); the AFP level decreased in all patients post treatment ($P = 0.01$), especially in the SVRs ($P < 0.01$). In multivariate analysis, hepatic fibrosis was a predictor of response to treatment ($P = 0.02$), while body mass index (BMI) (25–30 kg m^{-2}), hepatic activity (A2), hepatic fibrosis stage (F2–F4) and fibrosis improvement were predictors of AFP difference ($P = 0.007$, 0.01, 0.012, <0.001, 0.030, and 0.018), respectively. The diagnostic performance to predict the HCV treatment response was best by adding both AFP and hepatic fibrosis stage factors; the best cut-off value for AFP was 3.57 ng dl^{-1} with 50% sensitivity and 68% specificity with area under the curve (AUC) of 0.55 and for hepatic fibrosis stage was 3, with a sensitivity of 88%, a specificity of 30% with an AUC of 0.58.

Conclusion: In chronic HCV-infected patients, serum AFP below 3.57 ng dl^{-1} and hepatic fibrosis ⩽stage 3 are expected to have good response to treatment; BMI (25–30 kg m^{-1}), A2, fibrosis >2 and fibrosis improvement predict AFP change post treatment.

Introduction

Alpha-foetoprotein (AFP) is an α_1-globulin secreted by foetal hepatocytes and in a small amount by other cells of the foetal gastrointestinal tract. Physiologically, in human adults an increased AFP level is present in the serum of pregnant women [1]. The normal adult serum AFP concentration does not exceed 6 ng ml^{-1} [2]. Significant synthesis of AFP commences again when some adult cell becomes transformed to cancer cells and differentiated into adult hepatocytes [3]. Evaluation of serum AFP level and liver ultrasonography are the most widely used tools for screening

Abbreviations: U/L, unit/litre; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; HBsAb, hepatitis B virus surface antibodies; HBcAb, hepatitis B virus core antibodies; AUC, area under the curve; ROC, receiver operator curve; SVR, sustained virological response.

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of hepatocellular carcinoma (HCC) [4]. Elevations of serum AFP >20 ng l^{-1} were present in patients with hepatitis C virus (HCV)-related cirrhosis but without HCC with a prevalence ranging from 10% to 43% [5–7].

Factors associated with raised AFP include severity of liver disease, female gender and black race [8]. Serum AFP levels decline during hepatitis C long-term treatment against cirrhosis (HALT-C) antiviral therapy [9]. In patients with chronic HCV, elevated serum AFP levels were significantly correlated with lower serum albumin levels, advanced fibrosis/cirrhosis and genotype 1b infection [1]. HCV infection is a major health problem in Egypt, where the seroprevalence is 10–20-fold higher than that in the United States [10]. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to >40% among regions and demographic groups [11]. The overall prevalence of antibody to HCV in the general population is around 15–20%, [12] while the overall prevalence of anti-HCV antibody in semirural and rural Egyptian communities was 20.7%, and the prevalence in each type of community was 23% and 17.9%, respectively [13]. Arthur et al. [14] found that HCV seroprevalence in different governorates ranged from zero to 38% [14]. The seroprevalence of HCV increased with age, from 19% in persons 10–19 years old to about 60% in persons 30 years and older [15]. The main objective of this study was to verify the possibility of using AFP as a predictor of response to interferon–ribavirin (IFN–RBV) therapy in chronic HCV-infected patients.

Patients and methods

This study included 175 non-cirrhotic chronic hepatitis C (CHC) Egyptian patients, scheduled to receive the standard of care (SOC) antiviral therapy for 48 weeks; 91 patients received pegylated interferon (PEG-IFN) alpha 2b, 100 μg weekly (PEG intron, Schering Plough) and RBV (800–1000 mg) (Rebetol, Schering Plough) for 48 weeks and 84 patients received IFN alpha 2b, 3 MIU three times/week and RBV (800–1000 mg) for 48 weeks. Patients were recruited from the Hepatology Outpatient Clinic, Endemic Disease Hospital, Faculty of Medicine, Cairo University, after getting an informed written consent. A questionnaire was completed for every patient. Patients were excluded if they presented with other chronic liver disease, decompensated liver disease or HCC. HCV was diagnosed by detecting HCV antibody using the third-generation immunoassay (enzyme immunoassay, EIA) and confirmed by polymerase chain reaction (PCR) for HCV RNA. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total and direct bilirubin, complete blood count, albumin, prothrombin time and serum antinuclear antibody (ANA) were assessed using the standard methods. Serum AFP was quantitatively assessed using the CanAg AFP EIA enzyme immunometric assay kit (Fujirebio Diagnostics AB, Göteborg, Sweden). All patients had a baseline liver biopsy and only 79 patients had repeated serum AFP and liver biopsy at week 72. Both core biopsies (baseline and follow-up) were >10 mm in length and contained at least eight portal tracts. The specimen was stained with haematoxylin–eosin and Masson's trichrome for collagen. Specimens were examined by a hepatopathologist blinded to the patient characteristics. The liver fibrosis stage and necroinflammatory injury were assessed according to the Ishak modification of Knodell and METAVIR scoring systems [16,17]. Macrovesicular steatosis was classified into the following grades: 0 (no fatty infiltration), I (up to 33% of hepatocytes affected), II (>33–66% of hepatocytes) and III (>66% of hepatocytes) [18]. All patients were followed up for at least 6 months after treatment completion in order to assess their sustained virological response (SVR). Histologic response was defined as a decrease of at least one point in the fibrosis (staging) or steatosis scores or of at least two points in the activity score (grading), relative to the baseline biopsy score [19,20].

The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guideline.

Statistical analysis

Patients were classified according to their response at week 72 into respondents (SVR) and non-respondents (non-SVR). Quantitative variables were expressed as mean ± standard deviation (SD) for parametric data and median for non-parametric data. Qualitative variables were expressed as frequency and percentage. The Wilcoxon test was used to assess the pre- and post treatment AFP levels. Non-parametric data were transformed into their log values to submit correlation and regression analysis to correlate AFP with the different variables. Patients were classified, based on their median AFP levels, into two groups for regression analyses. Univariate and multivariate logistic regressions were used to assess the association between baseline AFP before treatment, AFP changes and different variables, while controlling for others. Regressions were also used to assess the association of response to treatment with other variables.

Results

This study included chronic HCV-infected patients ($n = 175$), who received the SOC antiviral therapy for 48 weeks. The age ranged between 21 and 58 years with a mean of 40 ± 9 years and male predominance ($n = 137$; 78.3%). The median baseline serum AFP value was 3.2 ng ml^{-1} for all patients ($P < 0.01$). Hepatitis B core antibodies (HBcAb) were positive in 38.9% and hepatitis B surface antibodies (HBsAb) were positive in 22.3%.

Table 1 shows the baseline demographic features and liver biochemical and haematological profiles of the studied patients in relation to the different AFP levels.

There was a significant association between baseline AFP level and baseline hepatic fibrosis stage as well as the response to treatment in a way that 78% of patients with mild to moderate liver fibrosis (F2-F4) had normal AFP at baseline ($P = 0.004$) (Table 2). Similarly, 77% of the non-SVR group had high AFP at baseline (P=0.04) (Table 2). Nevertheless, the Non-SVR group showed a high significant correlation of the raised AFP with the marked stage of fibrosis ($r = 0.584$, $P < 0.001$) and HAI grading ($r = 0.494$, $P = 0.003$) before treatment.

There was a significant histopathological improvement in the hepatic fibrosis and the Histological Activity Index (HAI) at week

Table 1
Baseline data of the studied patients in relation to AFP Levels.

	Normal AFP (mean ± SD)	High AFP (mean ± SD)	*P* value
Age years	39.27 ± 8.42	43.36 ± 8.14	**0.034**
Laboratory			
Albumin (gm dl^{-1})	4.22 ± 0.41	3.99 ± 0.31	**0.014**
AST × ULN (IU l^{-1})	1.67 ± 1.08	2.61 ± 1.13	**<0.001**
ALT × ULN (IU l^{-1})	1.87 ± 1.03	2.30 ± 1.14	0.071
ALP × ULN (IU l^{-1})	0.70 ± 0.22	0.82 ± 0.25	**0.016**
Platelets (×10^3/mm^3)	227.31 ± 67.57	175.14 ± 51.82	**<0.001**
Viral load (×10^6)	0.28 ± 0.25	0.39 ± 0.39	0.158
HBcAb ($n = 166$)			
Positive	90 (62.5%)	8 (36.4%)	**0.03**
Negative	54 (37.5%)	14 (63.6%)	

Abbreviations: AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HBcAb, Hepatitis B core antibody.
AFP level was higher at baseline in patients with: older age ($P = 0.034$), lower albumin (0.014), higher AST (<0.001), higher ALT (0.016), lower platelets (<0.001) and positive HBcAb ($P = 0.03$).

Table 2
Baseline hepatic Fibrosis stages and response to therapy in relation to the AFP level ($n = 175$).

	AFP at baseline		Total (%)	*P* value
	Normal AFP (<10 ng ml^{-1}) ($n = 153$) (%)	High AFP (⩾10 ng ml^{-1}) ($n = 22$) (%)		
Fibrosis stages				
No-minimal (F0, F1)	17 (11.1)	1 (4.5)	18 (10.3)	$P = 0.004$
Mild (F2–F4)	120 (78.4)	13 (59.1)	133 (76.0)	
Marked (F5, F6)	16 (10.5)	8 (36.4)	24 (13.7)	
Results after SOC therapy				
Non-SVR	83 (54.2)	17 (77.3)	100 (57.2)	$P = 0.04$
SVR	70 (45.8)	5 (22.7)	75 (42.8)	

Abbreviations: AFP, Alpha-fetoprotein.
Table 2 showed that 78% of patients with mild to moderate fibrosis stages (F2-F4) had normal AFP ($P = 0.004$) and 77% of patients of non-SVR group had high AFP ($P = 0.04$) before treatment.

72 post treatment in the SVR group ($P = 0.013$, $P = 0.002$, respectively). No change was observed in the hepatic steatosis in both groups (Table 3). Moreover, the level of liver fibrosis improvement correlated with the declined AFP levels post-treatment ($r = 0.255$, $P = 0.023$).

There was a post-treatment decline in the AFP levels in all groups and this level was significantly decreased in the SVR group, $P < 0.01$ (Table 4).

The total SVR was 75/175 (42.9%), while the total number of non-respondents is 100/175 (57.1%) with 11 (6.3%) discontinued due to serious side effects and 13 (7.4%) withdrawn from the study. The type of combined IFN/RBV therapy showed non-significant difference with AFP levels ($P = 0.11$ (NS), $P = 0.35$ (NS)).

Table 3
Liver biopsy in relation to treatment response at week 72.

Liver biopsy at 72 weeks	Response at 72 weeks			*P* value
	Non-SVR (%)	SVR (%)	Total (%)	
Fibrosis at 72 weeks				
Worse	7 (46.7)	3 (10)	10 (22.2)	
Same	5 (33.3)	11 (36.7)	16 (35.6)	0.013
Improved	3 (20)	16 (53.3)	19 (42.2)	
HAI at 72 weeks				
Worse	6 (40)	2 (6.7)	8 (17.8)	
Same	3 (20)	1 (3.3)	4 (8.9)	0.002
Improved	6 (40)	27 (90)	33 (73.3)	
Steatosis at 72 weeks				
Worse	1 (6.7)	3 (10)	4 (8.9)	
Same	5 (33.3)	16 (53.3)	21 (46.7)	0.33
Improved	9 (60)	11 (36.7)	20 (44.4)	

Abbreviations: SVR, sustained virological response.
Table 3 showed that in the SVR-group, 53% had regression of the liver fibrosis stages ($P = 0.013$) and 90% had improved HAI ($P = 0.002$) after treatment. No change was observed in liver steatosis in both groups.

Table 4
Pre- and post-treatment AFP levels in relation to treatment response (week 72) ($n = 79$).

AFP groups	Pre-treatment		Post-treatment		*P* value
	Mean ± SD	Median	Mean ± SD	Median	
AFP in all patients ($n = 79$)	5.4 ± 7.9	3.23	2.77 ± 7.5	0.50	<0.01
AFP in non-SVR ($n = 33$)	6.1 ± 7.6	3.30	3.79 ± 7.4	0.58	<0.01
AFP in SVR ($n = 46$)	4.9 ± 8.2	3.11	2.04 ± 7.6	0.49	<0.01

Abbreviations: AFP, alpha-fetoprotein; SVR, sustained virological response.

In univariate analysis, by binary logistic regression analysis in which the response to treatment is the dependent variable the AFP level was a good predictor of response ($B = -0.29$, $P = 0.04$) as was hepatic fibrosis stage ($B = -0.36$, $P = 0.02$).

Nevertheless, in a multivariate regression analysis AFP, age, platelets, fibrosis stage and HAI were the independent variables; fibrosis stage was the only predictor for response to treatment ($B = -0.39$, $P = 0.01$).

In multivariate analysis in which the baseline AFP level was the dependent variable, BMI >30 kg m^{-2}, high-grade fibrosis (F3) as well as marked steatosis were the significant independent factors (*P*: 0.03, 0.03, and 0.04, respectively).

In multivariate analysis in which the baseline AFP difference was the dependent variable, BMI (25–30 kg m^{-2}), baseline inflammation Grade A2, baseline fibrosis stages (F2, F3 and F4) and fibrosis improvement were the predictors for AFP difference ($P = 0.007$, 0.01, 0.012, <0.001, 0.030, and 0.018, respectively) (Table 5).

By using the receiver operator curve (ROC) for AFP alone to predict the treatment response, no good reliable cut-off value was obtained. However, by using the AFP level and hepatic fibrosis

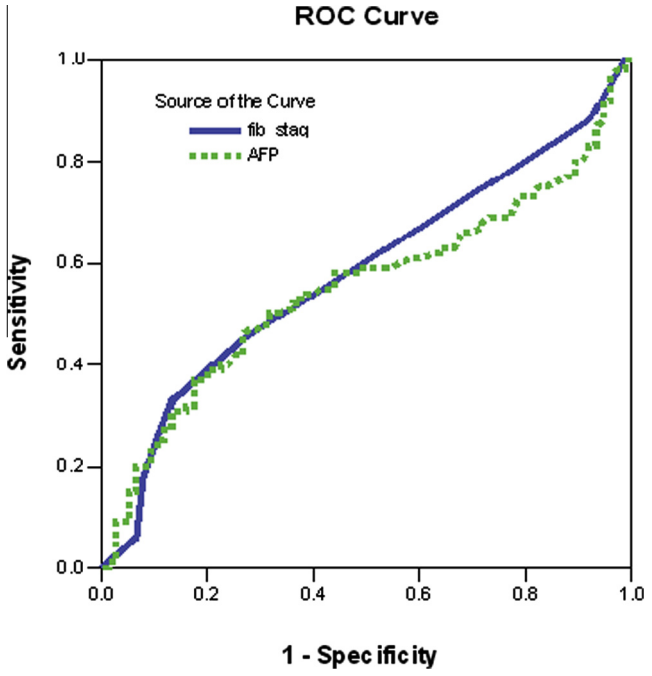

Fig. 1. ROC curve for AFP and hepatic fibrosis in relation to treatment response.

Table 5
Factors independently associated with elevated AFP difference in the multivariate analysis.

		Multivariate analysis		*P* value
		Odds ratio (OR)	95% confidence interval (CI)	
Body mass index (BMI)	25–30	0.13	0.03–0.57	**0.007**
Baseline inflammation	A2	29.5	2.1–39.8	**<0.01**
Baseline fibrosis stages	F2	0.05	0.01–0.52	**0.012**
	F3	0.002	0.05–0.07	**<0.001**
	F4	0.030	0.0013–0.72	**0.030**
Fibrosis improvement		0.144	0.029–0.72	**0.018**
SVR group		4.641	0.81–26	0.085

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; SVR, sustained virological response.
Table 5 showed that the multivariate analysis where AFP difference is the dependent variable, BMI (25–30 Kg/m2) ($P = 0.007$), baseline inflammation A2 ($P = 0.01$), baseline fibrosis stages (F2, F3 and F4) (0.012, <0.001, 0.030) and the

stage to predict the response to treatment, the best cut-off value for AFP level was 3.57 (0–10 ng ml^{-1}) at a sensitivity of 50% and a specificity of 68% with an area under the curve (AUC) of 0.55 and the best cut-off for fibrosis stage is 3 (Knodell) at a sensitivity of 88% and a specificity of 30% with an AUC of 0.58 (see Fig. 1).

Discussion

The response of CHC to treatment is not uniform across all populations [22] and is dependent on various viral and host factors. Several studies have recommended the AFP to be added to the list of factors predictive of treatment response in CHC including genotype-4 [23–25]. AFP > 17.8 ng/dl is highly specific for the diagnosis of liver cirrhosis in patients with hepatitis C [21].

This study showed that AFP levels were found to be elevated in 12.6% in the Egyptian CHC patients with 10 ng ml^{-1} upper limit of normal (ULN). Studies reported elevated AFP values with levels ranging between 10 and 30 ng ml^{-1} ULN, with variable prevalence [1,6–8,26].

Studies have concluded that the SVR rate was higher among patients with serum AFP levels below rather than above the median value 5.7 ng ml^{-1} [23,24] and have confirmed the value of serum AFP levels in predicting treatment outcome in CHC patients, regardless of the infecting genotype [23]. The present study showed that when AFP at/below a cutoff 3,57 ng/dl, associated with mild liver fibrosis stage F3 before treatment, a higher SVR for this group of patients is expected. However, the specificity and sensitivity at this cutoff is not high. However, this cut-off value is lower than those suggested by previous studies [23,25].

In this study, the SVR group showed a highly significant correlation between the baseline AFP and the age. Advance of age is associated with progression of liver disease, impairment of liver function and progression of fibrosis. This is in agreement with other studies showing that age has a significant correlation with AFP in affecting response to treatment (SVR) [24,27]. However, this is not in agreement with Seifi [28], who showed no significant correlation between age and AFP in anti-HCV-positive haemodialysis patients [27,28].

The non-SVR patients showed a significant positive correlation between baseline AFP and baseline AST and ALP but not with ALT. These results are not in agreement with those studies illustrating that ALT >150 versus $\leqslant$150 U l^{-1} was associated with elevated AFP levels [26] but with others showing that AST level was a predictor of response to therapy in chronic HCV with AFP [27,29]. However, Al Ashgar [30] demonstrated that only lower baseline serum AST, not ALT, is an independent predictor of SVR to PEG-IFN alpha-2a and RBV in patients with chronic HCV genotype-4. This relation between AST and AFP reflects pathological changes in the liver rather than hepatic injury [30].

The low baseline AFP had a significant correlation with normal platelet count in the SVR group; this is in agreement with other studies [9,26]. Chen et al. [27] showed that CHC patients without HCC, showing a low platelet count, have elevated serum AFP levels. These results may be attributed to the presence of chronic liver disease with subsequent cirrhosis, the progressive deterioration of the liver condition and impairment of the liver biochemical profile leading to elevated liver enzymes and thrombocytopaenia [29]. Jurczyk et al. [31] in their results, showed no significant differences in either end-of-treatment response (ETR) or SVR in HCV patients [31]. Studies showed that elevated serum AFP levels were significantly correlated with lower serum albumin levels; [1] this is in agreement with our results.

The baseline AFP is significantly higher in the group with marked hepatic fibrosis stages (F5–F6) of both groups pre-treatment and a highly significant correlation in the non-SVR group post treatment ($P = 0.000$), so that the higher the pre-treatment AFP levels, the more advanced the stage of hepatic fibrosis, and the lower the SVR, which is agreement with Tai et al. [26]. In this series, the post-treatment liver biopsy at 72 weeks showed improvement of the hepatic fibrosis stages and HAI, mainly in the SVR group.

Baseline hepatic fibrosis stage F3 showed a higher presentation in the non-SVR group than in the SVR group while the baseline stage F1 was higher in the SVR group than in the non-SVR group. These results are consistent with results of the Chinese study concluding that among genotype 1b patients fibrosis stage >F3 is an independent predictor associated with elevated AFP values [1] and with other studies stating that among genotype 4 CHC patients, severe fibrosis (Metavir score >F2) and a high serum AFP level were all negatively associated with SVR and recommended the use of pre-treatment serum AFP level in the routine assessment of factors predictive of a treatment response [4,24,29].

The baseline AFP was also significantly correlated with the pre-treatment hepatic inflammatory changes, with an HAI score of 5/6 ($P = 0.003$). We found also a highly significant correlation between response to treatment and HAI difference and HAI change percent: the higher the HAI difference and change percent, the lower the response to treatment. The higher is the baseline HAI, the higher the baseline AFP level and the lower the SVR. Thus, serum AFP level is a good predictor for HAI in liver biopsy. These results are in agreement with other studies [26,29] but are in disagreement with Chu et al. [1] who found that the necro-inflammatory activity had no effect on serum AFP in CHC patients [1]. However, no correlation was detected between the degree of hepatic steatosis and AFP level; these results are in agreement with other studies [4] but in disagreement with Gad et al. [24], who stated that among genotype-4 CHC patients, severe hepatic steatosis and a high serum AFP level were negatively associated with SVR [24].

The baseline AFP levels were higher in the non-SVR group and decreased after treatment with PEG-IFN/RBV in both groups and this was more evident in the SVR group, which is lower than reported by the previous studies [23,25]. These results are in agreement with other studies [23–25,32]. A highly significant correlation was detected between the baseline AFP and the AFP difference in the SVR group.

In this series, no changes in liver biopsies were detected in relation to median AFP difference; however, the higher the AFP difference, the higher the fibrosis difference and change percent in the studied patients. It is worth mentioning that 41.8% and 75.9% of the patients showed improvement of hepatic fibrosis and HAI, respectively, in liver biopsies at 72 weeks post treatment with PEG-IFN/RBV. Similarly, the SVR group showed improvement of hepatic fibrosis and HAI post treatment ($P = 0.013$, 0.002).

Hepatic progenitor cell (HPC) expression has been associated with response to treatment, being higher in the non-respondents than in the respondents [33]. HPCs are detected in the periportal region of the liver and could be responsible for liver regeneration, expressing high levels of AFP [34–36]. Their presence is related to increased fibrosis stages [33] and their stimulation has been associated with activation of stellate cells and development of fibrosis [37]. The intense HPC expression is observed in non-respondents compared to respondents. This could explain the negative association between the high AFP levels, higher stages of fibrosis and the response to treatment in CHC.

In multivariate analyses, baseline F3 and BMI >30 kg m^{-2} were the predictors for pre-treatment AFP level while BMI (25–30 kg m^{-2}), baseline A2, baseline (F2, F3 and F4) and fibrosis improvement were the predictors for AFP difference.

The rate of SVR in the patients of our study was 42.9%, which is similar to data from Alfaleh et al. [38]. The relatively high virological response to combination therapy in our patients might be

attributed to good patient selection, proper storage of medications, meticulous follow-up and proper dose tailoring. Factors associated with SVR to IFN treatment have not yet been fully investigated in HCV genotype 4-infected patients. It would be useful to understand the factors predicting the response to IFN in order to optimise treatment indication and administration and consequently decrease the cost. Some pre-treatment predictors of response to IFN-based therapy have been well identified. HCV genotype, baseline HCV RNA viral load, level of fibrosis or cirrhosis, baseline ALT level, body weight and age have been reported to affect response to therapy [39]. In our study, baseline AFP concentrations appeared as a significant predictive factor for response to treatment. Higher response rates were associated with lower baseline AFP levels and higher AFP difference.

Conflict of interest

The authors declared that there was no conflict of interest.

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