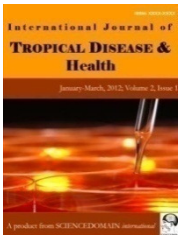

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Thrombocytopenia in Egyptian Patients with Hepatitis C Virus Treated with Standard of Care Therapy: A Cohort Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EM and GE performed the conception and design of the study. Authors RM and ZZ performed the analyzing the results and drafting the manuscript. Authors MEB and MS performed the revision of the manuscript. Author FA performed the data collection, enrollement and clinical assessment of the selected patients. All authors read and approved the final manuscript.

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ABSTRACT

Background and Study Aims: Thrombocytopenia (TP) in chronic hepatitis C virus (HCV) is a common finding either directly due to viral infection of platelets or indirectly due to

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immune alteration triggered by the virus, the consequences of HCV- induced cirrhosis and portal hypertension, or induced by Interferon (IFN), the corner element of the standard of care (SOC) therapy for HCV. This study aimed to evaluate TP in patients with chronic HCV, and to evaluate the mutual effect between SOC and TP.

Methods: The study was conducted on 209 patients with chronic HCV from Railway Hospital, Cairo. Patients were divided into two groups, Group (I): 144 patients who received SOC therapy, and Group (II): 65 patients who did not receive therapy. All patients were subjected to clinical examination, laboratory investigations, abdominal ultrasonography, and liver biopsy.

Results: TP was a common finding (60/209; 28.7%), more in group I (33/ 60; 55%, mean= 124.8±16.2/ml), and was significantly worse in group II (mean= 99.7±36.3/ml, p=0.008). Along the course of treatment, 2 significant drops of platelet count took place, nadirs at W8 and W24. TP was significantly related to hepatitis activity and hepatic synthetic function, and not related to the viral load. Four cases developed severe TP, only 1 of them continued therapy on IFN dose reduction.

Conclusions: TP is a common complication among HCV patients and along its SOC therapy, particularly influenced significantly by splenomegaly and advanced fibrosis.

Keywords: Hepatitis C Virus (HCV); Thrombocytopenia (TP); Standard of Care (SOC); Interferon (IFN).

1. INTRODUCTION

Platelet count in HCV patients was significantly lower than in the HCV-negative patients (P<0.02) [1], for several factors e.g defective platelet production due to decreased production of thrombopoietin (TPO) [2-3], cross-reactivity of anti-platelet glycoprotein antibodies and viral antibodies, accelerated platelet clearance due to immune complex disease [3], splenic pooling of platelets due to portal hypertension [3-4] and the hepatitis C viral detection peripherally in blood platelets [5]. This later finding suggested the potential direct role of HCV on TP [6]. Thus, treatment with IFN-α significantly increased it [7]. However, TP complicates antiviral treatment, particularly among cirrhotic patients [8]. An Egyptian study showed that fibrosis stage and weeks 2 and 4, were independent predictors of hematological parameters' reduction, which were not related to SOC [9].

1.1 Objective of the Work

Main objective: To evaluate TP in patients with chronic HCV received SOC therapy (PEG/ IFN and RBV) in comparison to those who did not. Sub objectives: To assess both; effect of IFN therapy on platelet count, and conversely the impact of TP on treatment plan, whether initiation or completion.

2. PATIENTS AND METHODS

209 patients with chronic hepatitis C (CHC) who presented to Railway Hospital, Cairo from June 2010 till May 2011, seeking for antiviral SOC therapy according to AASLD guidelines, 2009 [10]. They were subdivided into two groups. Group I: patients who were received SOC therapy, and Group II: patients who did not receive it.

Inclusion criteria:

- Adult (≥18 years old) patients
- Documented chronic HCV infection by a) Positive anti-HCV and b) Positive by HCV RNA.

Exclusion criteria:

- Any other cause of liver disease i.e other than HCV.
- History or currently receiving IFN therapy.
- Decompensated liver disease.
- Hepatocellular carcinoma (HCC).
- Hypersenstivity to IFN or RBV.

This study was approved by the Department Ethical Committee and a signed written informed consent was taken from all patients before starting treatment.

All patients were subjected to: Thorough history taking, and clinical examination.

2.1 Investigations Done

Laboratory tests: 1) Complete blood count (CBC). TP, defined as a platelet count of <150.000/mm^3 [11], was classified, in this study, as mild with platelet count 100-150 x 10^3 / mm^3, moderate at 50-100 x 10^3 / mm^3 and severe with < 50 x 10^3 / mm^3. 2) Liver biochemical profile (LBP): transaminases; aspartate aminpotransferase (AST), and alanine aminotransferse (ALT), alkaline phosphatase (ALP), serum albumin, total bilirubin, prothrombin concentration (PC). 3) Kidney function tests (blood urea & serum creatinine). 4) Fasting and 2 hours post prandial blood glucose. 5) Alpha fetoprotein (AFP), antinuclear antibody (ANA), thyroid stimulating hormone (TSH). 6) Hepatitis seromarkers for HCV (anti HCV) and for hepatitis B virus (HBV); (HBsAg, anti HBc and anti HBs) using ELISA technique. 7) HCV RNA tested by PCR nested quantitative by IU/mL. 8) Rectal snip to diagnose active Schistosomiasis. 9) ECG (men over 40, women over 50).

Patients were globally evaluated by Child Pugh score [12].

Imaging: Abdominal ultrasonography by TOSHIBA®, Japan. Splenomegaly is considered if >12cm in females & >13cm in males [13].

Histopathological examination by ultrasound guided liver biopsy such that PC ≥ 60% and platelet count ≥ 60.000 / mm^3 according to METAVIR scoring system [14].

Upper endoscopy by Olumpus®, USA, was done for all cirrhotic patients to evaluate oesophageal +/- gastric varices according to AASLD practice guidelines, 2007 [15].

Group I were followed up during anti-viral therapy (for 48 weeks), clinically by weekly symptoms checklist, and by laboratory testing :a) CBC done every 4 weeks for 24 weeks then at the end of treatment. b) PCR for HCV RNA at start of therapy, 12, 24 & 48 weeks of therapy.

Statistical Analysis Patients' data were analyzed using SPSS 17.0 for windows 7. Quantitative variables were expressed by mean and SD (Standard deviation), compared

using t-student and Mann-Whitney test, paired t-test and ANOVA test were used when appropriate. Qualitative variables were expressed by numbers (Frequency) and percent compared between groups using Chi square test and Fisher's exact test as appropriate. P value was considered to be significant if <0.05 and highly significant if <0.001.

3. RESULTS

The present study was conducted on 209 HCV naïve patients. They presented to Railway Hospital, Cairo, seeking for antiviral therapy from June 2011 till Sept. 2012. They were divided into Group I: 144 patients who received anti-viral treatment, and Group II: 65 patients who did not receive therapy.

Demographic features of the studied groups are shown in Table 1.

Table 1. Demographic features of the studied groups

Characteristic		Group I (n=144)	Group II (n=65)	Total	P value
Age in years (Mean ± SD)		45.5±7.0	45.4±10.0	45.5±8.2	0.59
Gender n (%)	Male	140 (97.2)	50 (76.9)	190	0.06
	Female	4 (2.8)	15 (23.1)	19	

The minority of Group II (6/65; 9.2%) were candidates for therapy but refrained from SOC therapy for the side effects that may take place as been informed or heard about from other patients who had already started therapy, the rest (59/ 65; 90.8%) were not fit. Causes of non-candidacy for treatment in group II are illustrated in Fig. 1. The commonest cause of non candidacy was the hepatic cirrhosis with portal hypertension (PH). They commonly presented with Child-Pugh grade A (14/22 patients; 63.6%), B (6 patients; 27.3%) and C (2; 9.1%), and small oesophageal varices were diagnosed in most of them (11 patients; 50%), medium varices in 8 patients (36.4%), and 3 patients had large ones (13.6%), and one of them had an extended gastric varix.

TP (moderate and severe) was 3rd cause (8 patients; 12.3%, mean =66000/ml). Mean Hb in anaemic patients (3; 4.6%) was 10.4gm/dl. Splenomegaly was significantly higher in group II than in group I (21/65; 32.3%, mean diameter= 14.7 cm, and 25/144; 17.4%, mean diameter = 16.8 cm respectively, P = 0.016).

One patient had positive rectal snip for Schistosomiasis for which he received Prazequintal before starting SOC. Some patients had more than one cause limiting SOC treatment, particularly those with F4 who had TP and anaemia.

Baseline laboratory data in the studied groups is shown in Table 2. All except total bilirubin, AFP and HCV RNA PCR, showed statistical difference between the 2 groups; particularly ALT & PC which were significantly higher in group I than group II with (P=0.001 & 0.004) respectively. Trasaminases were mildly elevated (<2 fold rise) in both groups.

Baseline laboratory findings of patients with TP among all the studied groups are shown in Table 3. TP was detected in 60 patients (28.7%). All labs except HCV RNA and ALT, showed significant difference between the two groups. TP in the 2 studied groups is shown in Table 4. TP was more in group I (33/60; 55%). The commonest grade of TP was the mild one (45/ 60; 75%), particularly in group I (31/33; 93.9%). On the contrary, severe TP was only present in group II (3/27; 11.1%) which precluded IFN therapy.

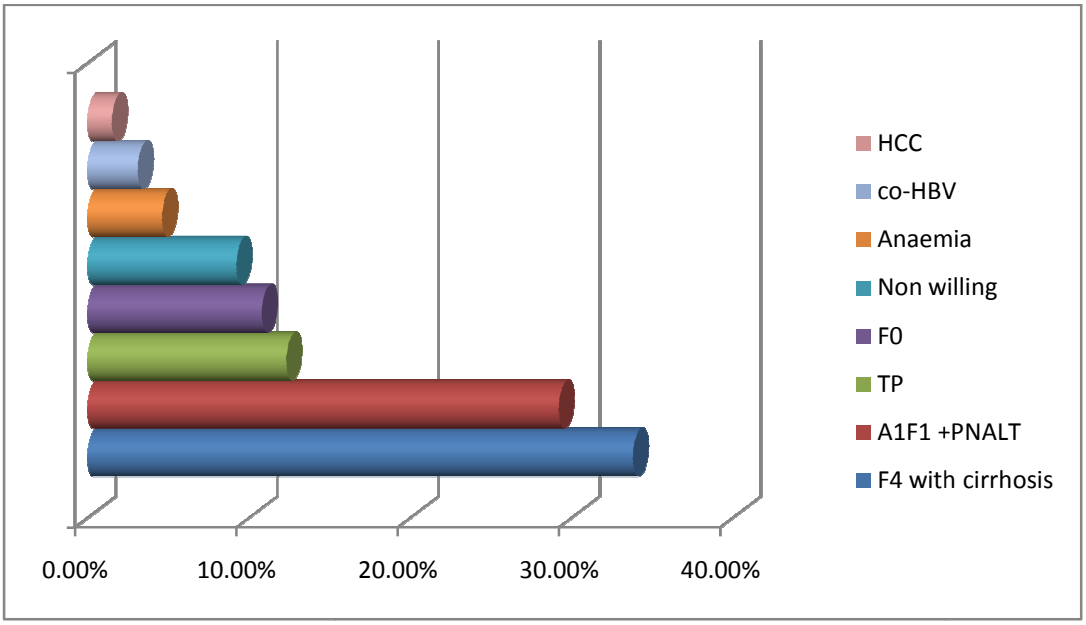

Fig. 1. Causes of not receiving SOC therapy in group II

Table 2. The baseline laboratory data of the studied groups

Laboratory result mean ± SD	Group I (n=144)	Group II (n=65)	P value
Total Bilirubin 0.1-1.2 mg/dl	0.83±0.31	1.04±1.03	0.522
ALT Up to 40 IU/L	81.2±54.0	49.4±29.9	0.001
AST Up to 40 IU/L	68.4±41.2	55.4±41.8	0.003
ALP (30-120 IU/L)	84.8±26.1	109.6±64.7	0.017
Albumin 3.5-5.2 g/dl	4.1±0.3	3.8±0.6	0.010
PC (%) 70-100%	96.6±7.0	86.8±17.4	0.004
Hb (14-16 g/dl)	14.3±1.2	13.3±1.7	0.001
WBCs $x10^3/mm^3$ (4-11)	6.6±2.1	5.5±2.3	0.001
Platelets count (150-440) x $10^3/mm^3$	192±56	170±73	0.004
AFP (0-8.1 ng/ml)	9.9±20.7	22.3±59.1	0.473
HCV RNA PCR IU/mL	987.219±2.569.013	1.624.112±2.910.533	0.366

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferse, ALP: Alkaline Phosphatase, PC: Prothrombin Concentration, Hb: Haemoglobin, WBC: White Blood Cells, AFP: Alpha Fetoprotein, HCV RNA PCR: Hepatitis C Virus Ribonucleic Acid detection by Polymerase Chain Reaction test.

The histopathological examination of group I patients is shown in Table 5. The commonest finding was A1 (81/144; 56.3%) for activity and F2 (53/144; 36.8%) for fibrosis. Six patients (4.2%) recorded F4who were enrolled for treatment for being compensated, 2 of them (1/3) had TP.

Platelet count along the course of SOC treatment is shown in Fig. 2.

Influence of fibrosis on TP along the course of treatment is illustrated in Figs. 3a and b. The higher the fibrosis stage, the lower the platelet count. The severer TP was among

patients with F4, markedly noticed at W16. Among patients with F2 and F3 who were more frequent in our study, lowest levels of platelet count were noticed at W16 and W8 respectively.

Table 3. Baseline laboratory data in patients with TP and those without

Laboratory parameter		Patients with TP in both groups (n=60)	Patients without TP (n=149)	P value
Serum albumin	3.5-5.2 g/dl	3.8±0.6	4.1±0.35	0.01
AST	Up to 40 IU/L	76.9±45.4	59.3±39.1	0.001
ALT	Up to 40 IU/L	80.8±55.3	67.5±47.3	0.08
Bilirubin	0.1-1.2 mg/dl	1.12±1.06	0.8±0.3	0.001
WBCs	(4-11 x 10^3 / mm^3)	6.0±2.3	6.7±2.1	0.045
PC %	(70-100%)	88.2±17	95.7±9	0.001
ALP	30-120 IU/L	112.4±65.2	84.5±27.1	0.008
AFP	0-8.1ng/mL	31.6±66.2	6.5±6.1	0.002
HCV RNA PCR	x 10^6 IU/mL	1.194±200	1.180±2.926	0.38

Table 4. TP in the studied groups

TP (n=60/209; 28.7%)		Group I (n=33/144; 22.9%)	Group II n=27/65; 41.5%)	P value
Absolute figure Mean ±SD	x10^3/mm^3	124.8±16.2	99.7±36.3	0.008
Grading N (%) and its mean value ± SD x 10^3 / mm^3	Mild	31 (93.9%) 126.8±143.3	14 (51.9%) 128.1±179.7	
	Moderate	2 (6.1%) 92.5±21.2	10 (37%) 79.3±14.5	0.001
	Severe	0	3 (11.1%) 35±95.4	

Table 5. Histopathological examination of group I

Histopathology N (%)		TP (n=33)	Total (n=144)
Histological activity index (HAI)	A1	16 (48.5%)	81 (56.3%)
	A2	14 (42.4%)	52 (36.1%)
	A3	3 (9.1%)	11 (7.6%)
Fibrosis	F1	9 (27.3%)	52 (36.1%)
	F2	12 (36.4%)	53 (36.8%)
	F3	10 (30.3%)	33 (22.9%)
	F4	2 (6.1%)	6 (4.2%)

Influence of splenomegaly on platelet count along the course of treatment is shown in Fig. 4. Patients with splenomegaly had lower platelet count than patients without splenomegaly. Lowest count was noticed at W 16.

Platelet count in relation to HCV RNA PCR is shown in Table 6. It is worth noting that patients who achieved negative viraemia at W 12 denoting early virologic response (EVR), 24 & 48 denoting end of treatment response (ETR) were 105 (72.9%), 90 (62.5%) and 78 (54.1%) respectively. Platelet count did not show a statistically difference related to the virologic response.

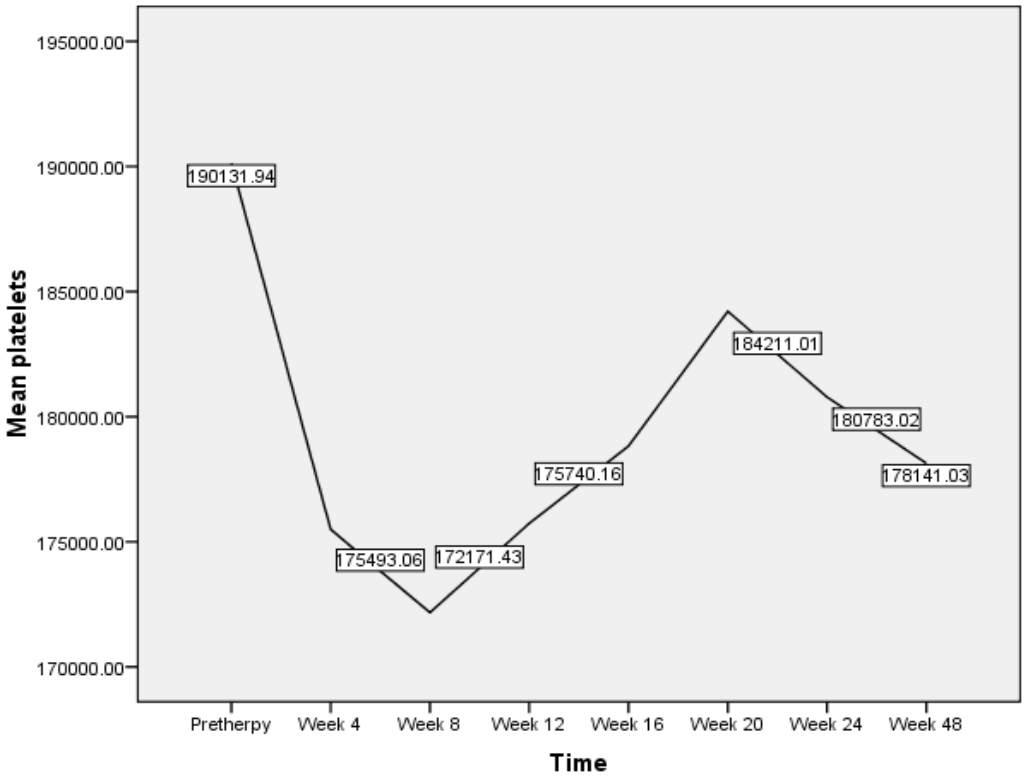

Fig. 2. Mean platelet count along the therapy in group I

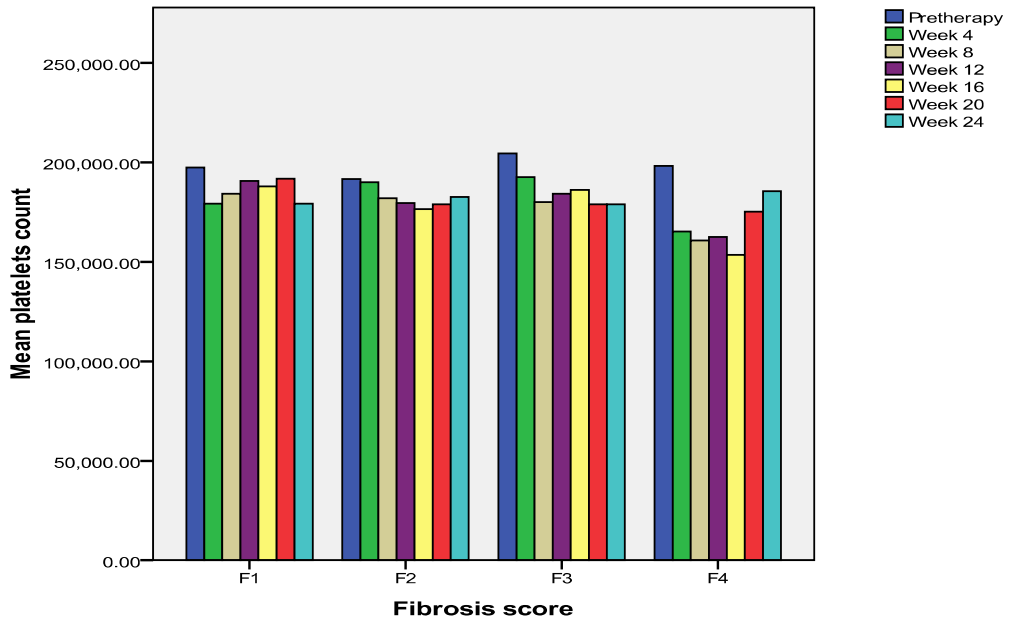

Fig. 3a. Influence of fibrosis stage on platelet count along therapy in group I

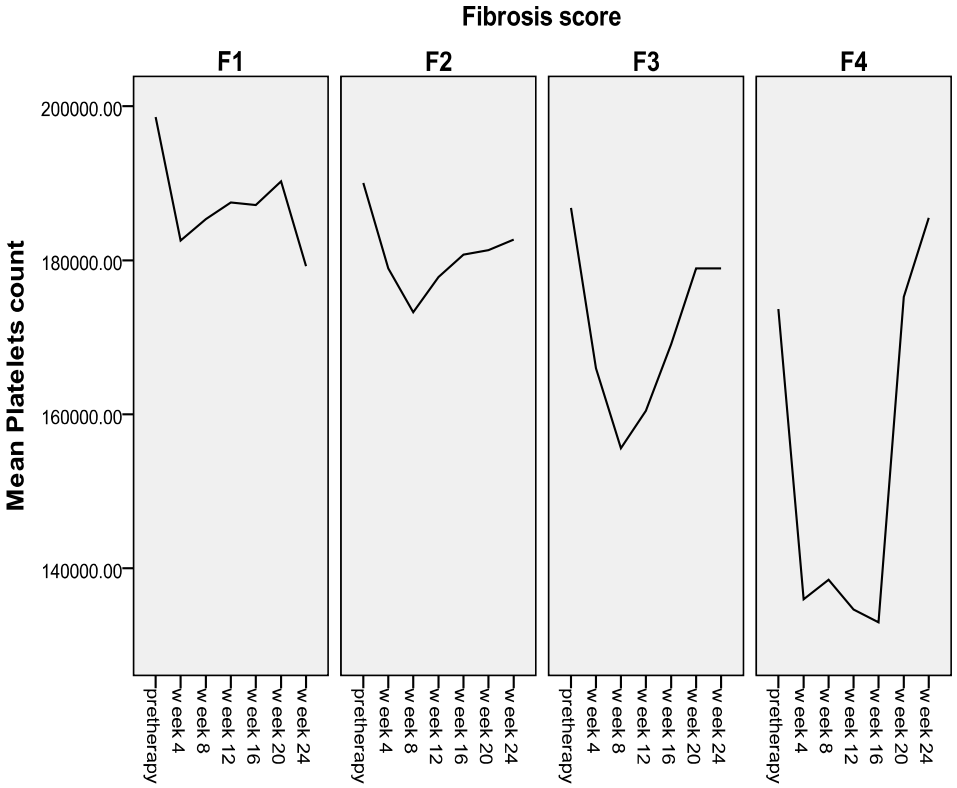

Fig. 3b. Influence of fibrosis stage on platelet count along therapy in group I

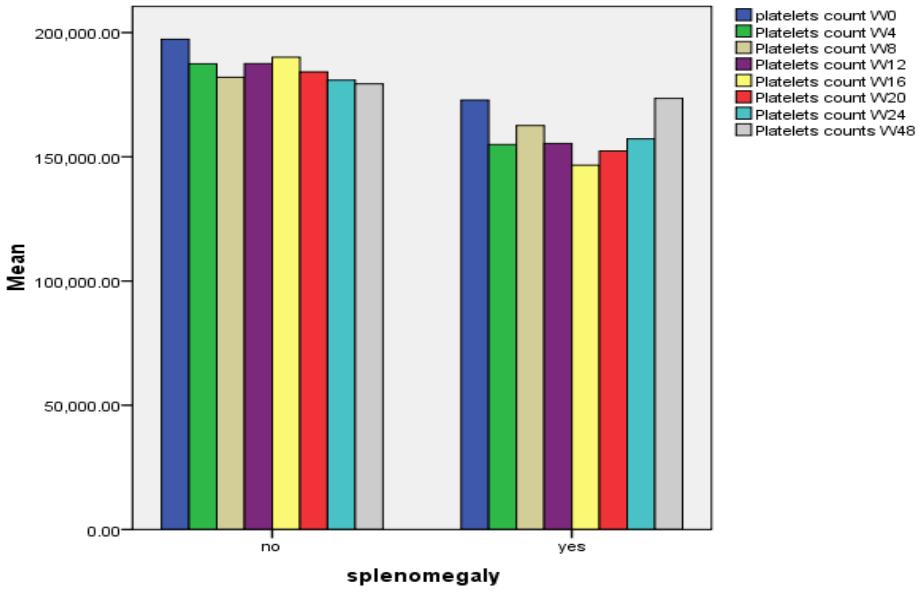

Fig. 4. Influence of splenomegaly on platelet count along therapy in group I

Table 6. Platelet count in relation to HCV RNA at W12, W24 and W 48

Week of therapy	Platelet count (Mean ± SD) X 10^3 / mm^3		P value
	.-ve PCR	+ve PCR	
W 12	193.3±55.5	183.3±61.3	0.4
W 24	195.0±56.4	207.9±51.4	0.31
W 48	180.8±63.4	169.2±65.1	0.28

In this study, 4 cases developed severe TP, most of them (3/4; 75%) had to stop treatment. The last one continued on dose reduction of IFN. The first 2 cases recorded severe TP preventing following doses [platelet count=43x10^3 / mm^3 at W4 (baseline platelet count 101x10^3 / mm^3 and F3), and 35x10^3 / mm^3 at W 8 (baseline platelet count 219x10^3 / mm^3 and F2) respectively].

The 3rd case developed severe TP in addition to positive viraemia at W 12 (platelet count=50x10^3 / mm^3, with baseline platelet count 91x10^3 / mm^3 and F4). The last case developed severe TP (48x10^3 / mm^3 at W16, baseline count 119x10^3 / mm^3 and F3) and continued on modified therapy.

4. DISCUSSION

Egypt has the largest burden of HCV infection in the world, with a 10% prevalence of chronic HCV infection among persons aged 15–59 years [16]. Pegylated IFN (PEG/IFN-α) combined with Ribavirin (RBV) had become the SOC- treatment in chronic HCV [17]. TP is a common haematological complication among patients with HCV related chronic liver disease (CLD). It has a negative impact on the evaluation of the disease, mainly in the advanced stages [18]. Also TP is associated with IFN use and is frequently observed among these patients [19].

This study aimed to evaluate TP in patients with chronic HCV who received SOC therapy and those who did not, and to assess the mutual influence of both of platelet count and SOC treatment. The study also addressed the relationship between platelet count and splenomegaly, various laboratory findings, HCV viraemia and stage of fibrosis.

Two hundred and nine patients with chronic HCV were included in this study. Sixty five patients did not receive treatment. One hundred forty four patients with chronic HCV who received SOC treatment, their mean age 45.5 years and there was male predominance for the fact that most patients who sought medical advice at Railway Hospital, Cairo were middle aged males, being employees, workers and drivers.

Unfortunately, in group II, the commonest cause of non candidacy for treatment was the late presentation (22/59; 37.3%) due to evident PH, secondary to advanced cirrhosis (F4), confirmed by the presence of esophageal and/ or gastric varices. This agreed with the fact that there is still a great deal of uncertainty surrounding the treatment of cirrhotic patients with SOC, as the sustained virological response (SVR) rates tend to be significantly lower [20], although Marco et al. [21] found no significant differences in treatment response among patients with and without esophageal varices (15.5 vs 21.1%; P = 0.3). Also, HCV- related decompensated cirrhosis should be referred for liver transplantation [7,22].

The second cause for non-candidacy for therapy was minimal necroiflammation and fibrosis. In patients with mild liver disease (F0-F1), particularly with long standing infection, a balance between the benefit and risk related to therapy must be struck, also taking into account the

perspective of new drugs and life expectancy of the patient [23]. ALT has been reported to increase during IFN therapy and this was apparently one major reason why the NIH Consensus Development Conference recommended that patients with persistently normal serum ALT (PNALT) not be treated with IFN [17].

In this study, moderate and severe TP precluding candidacy for SOC therapy constituted 3rd obstacle, which was higher in incidence and lower in mean count than Giannini et al. [24]; 12.3% and 66000/ml versus 6.5% and 90.000/mm^3 respectively.

Transaminases were significantly higher in group I than group II (P =0.001 &0.003 for ALT & AST respectively). This agreed with Ghany et al. [7] who recommended treatment in elevated ALT, as transaminases are the first biochemical abnormality detected in patients with liver disease, its degree of elevation may correlate with the extent of liver injury but is not of prognostic value [25].

In this study, the incidence of TP in the whole studied patients was 28.7% (60/209), which is slightly higher in group I, 22.9% (33/144). That figure was close to many studies reported prevalence of ≥ 24% [26-28].

Labs reflecting hepatocyte synthetic function i.e. albumin, bilirubin and PC were significantly worse in thrombocytopenic patients than those with normal platelet count. Similarly, hepatic enzymes reflecting inflammatory process, particularly AST, ALP and AFP were significantly higher in patients with TP than those with normal platelet counts. Thus, TP parallels hepatocyte inflammation and dysfunction in CHC, which was attributed to the impaired TPO production secondary to CLD and its degree of fibrosis [29-31].

On the other hand, there was no significant relation between TP and either ALT or HCV viral load, which was contrary to Olariu et al. [32] who showed a significant relation with both of them.

Regarding the liver histopathological findings of group I patients, we observed that the higher incidence of TP in patients with A1 and to a lesser extent in A2. On the other hand, TP was higher in patients with F2 and to a lesser extent in F3. This was different from previous results [29,32-35] which showed negative correlation between serum TPO levels and degree of liver fibrosis in HCV i.e TP occur with greater frequency and severity in patients with stages 3 or 4 fibrosis than in those with stages 0–2, accordingly, platelet count could be a surrogate marker to predict the stage of fibrosis, particularly at F3 and F4 [36] provided that there is no history of alcohol intake. Thus, patients who fulfill these criteria may not necessarily be candidates for liver biopsy. Similarly, Adinolfi et al. [34] found inverse relationship between TPO levels and liver fibrosis. In patients without splenomegaly, platelet count was the highest in those with fibrosis stage F1& F2, lower in those with stage F3and the lowest in those with stage F4. This may be explained by several points: a) results were biased by the selection of the patients in which inflammatory grades were commonly A1and F2 (48.5% and 36.4% respectively) according to EASL CPGs, treatment should be initiated in patients with advanced cirrhosis (METAVIR score F3-F4), and strongly considered in patients with moderate fibrosis (F2), b) TPO serum levels were correlated to fibrosis plus necrosis but not to the degree of inflammatory activity [29], and c) relative small sample size in each group, most evident in F4 cases in which TP were found in only 1/3 of them (2/6 patients).

IFN is one of the drugs inducing TP due to bone marrow suppression or platelet aggregation [37], or TPO suppression of its production or its secretion [38]. Regarding its effect on platelet count in this study, platelet count was affected mainly after 1st dose reaching lowest level at W8 then increased again till W20 (but still lower than pre treatment levels) then decreased at W24 again and reached lower levels at W48. This partially agreed with Fried et al. [39] who showed that with PEG/IFN, the platelet count decreased gradually over 8 weeks, stabilizing thereafter and returning to baseline values within 4 weeks of stopping therapy. Peck-Radosavljevic and colleagues, 1998 [38] demonstrated that the platelet count decreased by nearly 28% in subjects treated with at least one dose of standard IFN and PEG IFN. IFN-alpha treatment may also.

Studying the influence of fibrosis on platelet count along the therapy, TP was worst in those having F4, and nadir was recorded at W16. Lashin et al. [9] showed that fibrosis stage and platelet count at weeks 2 and 4 were independent predictors of TP ($p<0.001$ and 0.005, respectively), regardless the IFN type ($p = 0.79$).

As for the influence of splenomegaly on platelet count along SOC in this study, platelet count was lower in patients with splenomegaly and this is in agreement with many studies [34,40-41] which stated the inverse correlation between splenic size and platelet count in patients with HCV. Adding the effect of IFN treatment, lowest platelet count was observed in patients with splenomegaly at W16.

In this study we found no relation between HCV RVA viral load and TP either in untreated or in treated patients. That was contrary to Olariu et al. [32] who found a significant correlation between platelet count and viral load.

Eltrombopag, a TPO mimetic agent, became promising in HCV related TP and could be used prior to and during SOC therapy, thus decreasing the dose reduction and increasing the SVR, as concluded in an Egyptian study [42].

In the current study, along the course of SOC, 4 cases developed severe TP and required IFN stoppage and /or dose modification (4/144; 2.8%), only 1 patient continued on IFN dose reduction. This was slightly lower than that reported by Renou et al. [43] who stated that 4-6% of patients receiving SOC experienced TP with platelet counts falling below 50,000 requiring dose reduction or discontinuation of treatment. And also Sulkowski, [44] stated that TP, either pre-existed prior to, or complicated PEG-IFN, lead to dose modification in 19% of cases and discontinuation in 2% of cases.

Regarding the response to treatment in this study; EVR and ETR were reported in 72.9% and 54.2% respectively. These were slightly lower than that reported by El Raziky et al. [45] (89.1% and 64.1% respectively) and Taha et al. [46] with ETR 72.9%.

5. CONCLUSION

TP is a common complication among HCV patients and along its SOC therapy, particularly influenced significantly by splenomegaly and advanced fibrosis.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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