Study of thrombopoietin levels in some Egyptian patients with chronic liver diseases secondary to the hepatitis C virus

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Introduction
The hepatitis C virus (HCV) is a leading cause of chronic liver disease (CLD), cirrhosis, and hepatocellular carcinoma, as well as the most common indication for liver transplantation in many countries.

Purpose
This work was carried out to study of thrombopoietin (TPO) level in Egyptian patients with chronic hepatitis C and liver cirrhosis with HCV.

Patients and methods
This work was conducted on 40 patients proved to have chronic liver disease due to chronic HCV infection by positive HCV antibody by enzyme-linked immunosorbent assay, PCR for HCV RNA, abdominal ultrasonography, and histopathological examination. Twenty of these patients had chronic active hepatitis C (CAH) and the other 20 patietns had liver cirrhosis. Fifteen apparently healthy individuals (negative for HCV antibody) were included in a control group. None of the patients had received interferon therapy. Patients with other causes of CLD, chronic renal disease, diabetes, endocrinal hematological, and other debilitating diseases were excluded. All the patients studied were subjected to the following: complete medical history, full clinical examination, laboratory investigations including complete blood picture, liver function tests, fasting blood sugar, 2 h postprandial, HCV antibody and PCR for RNA of HCV; serum TPO level, abdominal ultrasonography, and liver biopsy for histopathological examination.

Results
Our results showed a highly significant reduction in the platelet count in patients with CAH (192.55 ± 41.02) and cirrhotic patients (159.800 ± 86.189) in comparison with (322.67 ± 38.12) the control group ($P < 0.01$). There was nonsignificant increase in TPO in patients with CAH (115.93 ± 71.66) and a significant decrease in TPO in cirrhotic patients (77.504 ± 64.576) in comparison with (107.98 ± 52.53) the control group. In the cirrhotic patients, there was a significant positive correlation between TPO and platelet count, whereas there was no correlation between TPO level and liver enzymes (alanine aminotransferase and aspartate aminotransferase) in all patients. In addition, a significant decrease in TPO was found in cirrhotic patients in comparison with CAH patients.

Conclusion
Serum TPO level was elevated in patients with chronic viral C hepatitis as a compensatory response to the reduction of platelet count with still functionally active liver cells, but as the disease progress to cirrhosis which also is associated with thrombocytopenia, TPO production is impaired, with failure to compensate the low platelet count aggravating thrombocytopenia.

Keywords:
chronic liver diseases, hepatitis C virus, thrombopoietin

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Introduction

The Hepatitis C virus (HCV) is a leading cause of chronic liver disease (CLD), namely, chronic hepatitis, cirrhosis, and hepatocellular carcinoma, as well as the most common indication for liver transplantation in many countries [1]. In 15–20% of acute HCV infections, the patient recovers spontaneously, but in the large majority of cases, the disease progresses to CLD [2].

Thrombocytopenia is a significant clinical problem in CLD patients in well-defined clinical scenarios including

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invasive diagnostic or therapeutic procedures, interferon treatment, bleeding esophageal varices, management of patients on orthotopic liver transplantation waiting lists, chemotherapy for solid tumors or hematological malignancies, and surgery [3].

Although the original theory by Aster suggested that thrombocytopenia can be exclusively attributed to increased pooling of platelets in the enlarged spleen caused by portal hypertension [4], many other factors are currently believed to be responsible for decreasing the platelet count in patients with CLD [5]. Thrombocytopenia depends on the stage of CLD, although the etiology of liver disease may also play a role. Two types of mechanisms may act alone or synergistically with splenic sequestration, thus causing thrombocytopenia. One is a central mechanism, which involves either myelosuppression because of hepatitis viruses or the toxic effects of alcohol abuse on the bone marrow, whereas the second mechanism is peripheral and involves the presence of antibodies against platelets [6]. More recently, the characterization of thrombopoietin (TPO) (megakaryocyte growth and development factor) and the results of studies aimed at evaluating TPO pathophysiology in patients with liver disease have shown a new scenario of the possible mechanisms of thrombocytopenia during the course of CLD [7].

The primary regulator of platelet production is TPO identified as the ligand for C-MPL [8]. TPO is a glycoprotein hormone produced mainly by the liver and the kidney. It stimulates the production and differentiation of platelets by the bone marrow [9]. The level of TPO is regulated by the total mass of platelets and megakaryocytes [10]. Its plasmatic clearance occurs by binding to MPL receptors expressed on megakaryocytes and platelets [9].

This work aimed to study the TPO level in Egyptian patients with chronic hepatitis C and liver cirrhosis with the HCV.

Patients and methods

This study included 20 patients with chronic active hepatitis C (CAH) (19 men and one woman, mean ± SD 45.20 ± 6.220 years) and 20 cirrhotic patients with an HCV infection (18 men and two women, mean ± SD 49.7 ± 9.02 years). None of the patients were receiving interferon therapy. Another 15 apparently healthy individuals matched for age and sex were included as a control group. None of them had any history or signs of liver diseases and they were HCV antibody negative. We excluded patients with chronic renal diseases, diabetes mellitus, other endocrinal disorders, autoimmune, and blood diseases. This study was carried out at the Internal Medicine Department, Al-Zahra Hospital, Al-Azhar University.

The diagnosis of CAH and liver cirrhosis in patients was made on the basis of the following: positive HCV antibodies by the enzyme-linked immunosorbent assay technique, confirmatory positive PCR for HCV RNA, and liver biopsy that showed the characteristic pathology of CAH or cirrhosis.

All patients and controls were subjected to the following:

(1) Full medical history.
(2) Thorough clinical examination.
(3) Abdominal ultrasonography.
(4) Laboratory investigations: 10 ml of blood was taken by venipuncture from each patient and control. The blood sample was divided into three tubes:
   (a) Two milliliters of blood was placed in 5 ml of EDTA solution for a complete blood profile using an automated hematological counter.
   (b) A volume of blood (1.8 ml) was placed in a 0.2 ml sodium citrate solution at a ratio of 1 : 9 for the estimation of prothrombin time and concentration.
   (c) The rest of the blood sample was placed in a tube and allowed to clot; serum was separated for the estimation of fasting blood sugar, liver function including serum transferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], albumin, total protein, and serum bilirubin, and a kidney function test including urea, creatinine, and electrolytes (Na^+ and K^+).
(5) TPO was determined using ELISA kits, which were supplied from R&D system (USA) by klin lab.

This assay uses the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for TPO is precoated onto a microplate, standards and samples are pipetted into the wells, and any TPO present is bound by the immobilized antibody. After washing any unbound substance, an enzyme-linked monoclonal antibody specific for TPO is added to the wells. Following a wash to remove any unbound antibody enzyme reagent, a substrate solution is added to the well and color develops in proportion to the amount of TPO bound in the initial step. The color development is stopped and the intensity of the color is assessed.

Statistics were calculated using Student's *t*-test. The correlation between two parameters in one group was determined using Pearson's correlation coefficient. A *P* value less than 0.05 was considered significant, whereas a *P* value less than 0.01 was considered highly significant.

Results

Our results showed a highly significant elevation of AST and ALT and total bilirubin in patient's groups when compared to the control group (Tables 1 and 2). There was significant decrease of serum albumin and nonsignificant decrease of PC in CAH patients group as compared to the control. While in cirrhotic patients, there was a highly significant decrease of serum albumin and significant decrease of PC as compared to the control group.

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The results showed significantly decrease and highly significant decrease of white blood cells and platelet count in CAH patients (Table 3) and cirrhotic patients (Table 4), respectively, in comparison to control. A nonsignificant difference was found in red blood cell and hemoglobin % between patients groups and control.

We found nonsignificant increase in the TPO level in CAH patients, whereas in cirrhotic patients there was a highly significant decrease in the TPO level in comparison with the control group (Table 5).

A nonsignificant correlation was found between TPO and serum transferases, serum bilirubin, and prothrombin concentration; whereas there was a significant positive correlation between TPO and serum albumin in group of CAH patients (Table 6). In cirrhotic patients, there was a significant and highly significant positive correlation between TPO and prothrombin concentration and serum albumin, respectively (Fig. 1 and Table 7). Also, there was positive correlation between TPO and platelets in cirrhotic patients (Fig. 2).

Our results showed a significant decrease in the TPO level in Child's A group in comparison with the control group, whereas Child's B and C groups showed insignificant differences from the control and from Child's A group (Table 8).

Table 1 Comparison of the results of liver function tests in patients with chronic active hepatitis C and healthy controls

	Mean ± SD				
Parameters	Patients ($n=20$)	Control ($n=15$)	*T* value	*P* value	Significance
AST	98.90 ± 70.26	25.67 ± 5.77	4.64	<0.01	HS
ALT	106.00 ± 56.40	23.53 ± 5.96	6.49	<0.01	HS
Bilirubin	1.01 ± 0.83	0.55 ± 0.24	2.35	<0.05	S
Albumin	4.01 ± 0.29	4.36 ± 0.38	2.88	<0.05	S
PT	13.54 ± 1.12	12.93 ± 1.08	0.15	>0.05	NS
PC	81.90 ± 14.4	84.67 ± 11.16	0.64	>0.05	NS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PC, prothrombin concentration; PT, prothrombin time.
S, significant <0.05.
NS, nonsignificant >0.05.
HS, highly significant <0.01.

Table 2 Comparison of the results of liver function tests in 20 patients with liver cirrhosis secondary to hepatitis C virus and healthy controls

	Mean ± SD				
Parameters	Patients ($n=20$)	Control ($n=15$)	*T* value	*P* value	Significance
AST	74.65 ± 28.74	25.67 ± 5.77	6.48	<0.0001	HS
ALT	77.86 ± 42.21	23.53 ± 5.96	5.43	<0.0001	HS
Bilirubin	1.815 ± 0.9022	0.55 ± 0.24	5.17	<0.0001	HS
Albumin	3.315 ± 0.6482	4.36 ± 0.38	6.02	<0.0001	HS
PT	14.83 ± 2.34	12.93 ± 1.08	3.20	<0.001	HS
PC	74.45 ± 20.12	84.67 ± 11.16	1.91	<0.05	S

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS, highly significant; PC, prothrombin concentration; PT, prothrombin time; S, significant.

Table 3 Comparison of complete blood count results in 20 patients with chronic active hepatitis C and healthy controls

	Mean ± SD				
Parameters	Patients ($n=20$)	Control ($n=15$)	*T* value	*P* value	Significance
WBCs	5.84 ± 1.17	9.01 ± 1.39	7.13	<0.01	S
RBCs	4.06 ± 0.66	4.07 ± 0.37	0.05	>0.05	NS
Hb	13.89 ± 1.25	14.01 ± 0.27	0.41	>0.05	NS
PLT	192.55 ± 41.02	322.70 ± 38.12	9.67	<0.01	S

Hb, hemoglobin; NS, nonsignificant; PLT, platelet; RBC, red blood cell; S, significant; WBC, white blood cell.

Table 4 Comparison of complete blood count results in 20 cirrhotic patients with hepatitis C virus and healthy controls

	Mean ± SD				
Parameters	Patients ($n=20$)	Control ($n=15$)	*T* value	*P* value	Significance
WBCs	4.895 ± 1.646	9.01 ± 1.39	7.79	<0.0001	HS
RBCs	3.795 ± 0.4045	4.07 ± 0.37	2.09	0.022	S
Hb	12.55 ± 2.345	14.01 ± 0.27	2.38	0.0115	S
PLT	159.80 ± 86.189	322.70 ± 38.12	8.14	<0.0001	HS

Hb, hemoglobin; HS, highly significant; PLT, platelet; RBC, red blood cell; S, significant; WBC, white blood cell.

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Table 5 Comparison of thrombopoietin results in chronic active hepatitis C patients, cirrhotic patients with hepatitis C virus, and healthy controls

	Mean ± SD				
TPO	Patients ($n=20$)	Control ($n=15$)	*T* value	*P* value	Significance
CAH patients	115.93 ± 71.66	107.98 ± 52.53	0.38	>0.05	NS
Cirrhotic patients	77.504 ± 64.576		5.30	<0.0001	HS

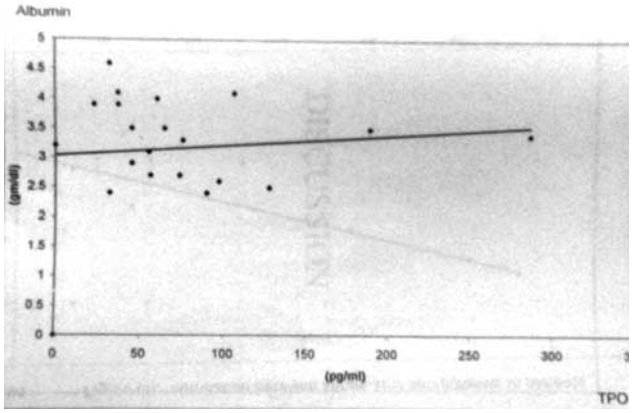
CAH, chronic active hepatitis C; HS, highly significant; NS, nonsignificant; TPO, thrombopoietin.

Table 6 Correlation between the thrombopoietin levels and liver function tests among the patients with chronic active hepatitis C

Parameters	TPO (*r*) value	*P* value	Significance
AST	−0.230	>0.05	NS
ALT	−0.050	>0.05	NS
Bilirubin	−0.180	>0.05	NS
Albumin	0.139	<0.05	S
PT	−0.194	>0.05	NS
PC	0.474	>0.05	NS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PC, prothrombin concentration; PT, prothrombin time; S, significant; TPO, thrombopoietin.

Figure 1



Positive correlation between serum thrombopoietin (TPO) and serum albumin in cirrhotic patients.

Table 7 Correlation between the thrombopoietin levels and liver function tests in the cirrhotic patients

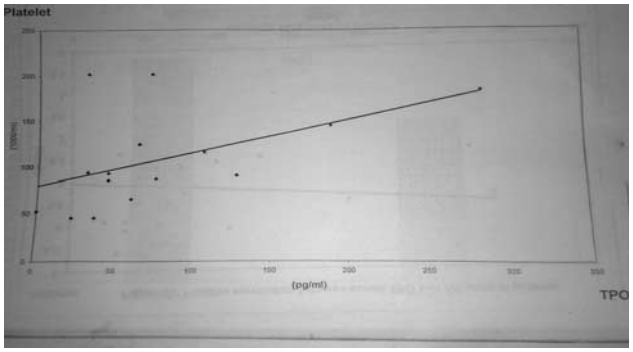
Parameters	TPO (*r*) value	*P* value	Significance
AST	0.4116	0.3554	NS
ALT	0.2216	0.022	NS
Bilirubin	0.4048	0.0115	NS
Albumin	0.771	<0.0001	HS
PT	−0.524	<0.05	S
PC	0.415	<0.05	S

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS, highly significant; NS, nonsignificant; PC, prothrombin concentration; PT, prothrombin time; S, significant; TPO, thrombopoietin.

Discussion

TPO is the major cytokine involved in the growth and development of megakaryocytes and the regulation of platelet production. TPO is produced by the liver at a constant rate and is cleared from circulation upon binding to its receptors (c-Mpl) on both megakaryocytes and platelets [11].

Figure 2



Correlation between serum thrombopoietin (TPO) and platelet count in cirrhotic patients.

In an alternative mechanism, TPO gene expression may be regulated by feedback control at the cellular level and TPO-mRNA levels may vary accordingly. Therefore, TPO serum level inversely correlates with the platelet and megakaryocyte mass [12], but in some thrombocytopenic conditions, the level of TPO is lower than would be expected by their platelet count [13].

Thrombocytopenia is one of the most frequent hematological abnormalities in patients with liver cirrhosis and portal hypertension. It is generally considered to be caused by increased sequestration and destruction of platelets in the enlarged spleen, which is associated with hypersplenism. As TPO is mainly produced in the liver, it is likely that a deficiency in this cytokine can account for the thrombocytopenia associated with advanced liver disease [14]. The proof for this is that portal decompression procedures, either by surgical shunts or transjugular intrahepatic portosystemic shunts, do not lead to a constant increase in the platelet count, and the only procedure that definitively results in the resolution of the thrombocytopenia of CLD is orthotopic liver transplantation [15].

Also, Goulis *et al.* [15] has shown that the TPO concentration is significantly low in cirrhotic patients with thrombocytopenia and there is a drastic increase in the TPO concentration in these patients starting from the first day after liver transplantation.

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Table 8 Comparison between thrombopoietin in different Child classes of liver cirrhosis and the healthy controls

	Control	Child A	Child B	Child C
Number of patients	15	7	8	5
TPO mean ± SD	108.55 ± 53.71	43.62 ± 33.59	85.81 ± 46.07	109.65 ± 105.86
T value	–	3.45	1.06	0.02
P value	–	< 0.05	> 0.05	> 0.05
Significance	–	S	NS	NS

NS, nonsignificant; S, significant; TPO, thrombopoietin.

In this study, we observed a significant decrease in the platelet count and an insignificant increase in TPO in patients with CAH in comparison with the control group. This result is not in agreement with that of Schoffski *et al.* [16], who reported that in patients with chronic viral hepatitis with minimal fibrosis, the serum TPO concentration was significantly elevated relative to the control group.

Thrombocytopenia in chronic hepatitis can be considered as an autoimmune mechanism as reported by Hernandez *et al*. [17]. TPO is the physiological factor mediating the feedback loop between circulating platelets and bone marrow megakaryocytes [18]. Therefore, the decreased platelet count may explain the high level of TPO as a compensatory mechanism by the liver with good synthetic function as reported by Sungaran *et al*. [19]. However, this stimulation is still insufficient to compensate for thrombocytopenia. This result is in agreement with the result of Stockelberg and colleagues [14,20], who reported an inverse relationship between circulating platelet mass and the TPO level. In addition, Long and Hoffman [21] reported that when the platelet count is high, TPO is taken up by platelets and megakaryocytes, resulting in a decrease in the circulating TPO level.

Our results showed a highly significant decrease in both the platelet count and TPO in the cirrhotic patients in comparison with the control group and in comparison with CAH patients. The low TPO response to the decreased platelet count in cirrhotic patients correlated with the serum albumin and prothrombin concentration (synthetic liver function). This is in agreement with Raquel *et al.* [22], who reported that serum TPO decreases with progression of the liver disease from minimal fibrosis to cirrhosis and concluded that besides impaired production in the failing liver, an increased TPO degradation by platelets sequestered in the congested spleen may contribute to thrombocytopenia in cirrhotic patients.

However, Shimodaira *et al*. [23] reported a constant plasma TPO level in liver cirrhosis and concluded that the thrombocytopenia in liver cirrhosis is not the result of a deficit in TPO production. Moreover, others have reported that serum TPO increased in chronic hepatitis C patients in response to the thrombocytopenia induced by interferon therapy [24].

The present study showed an insignificant correlation between TPO and both AST and ALT. Both enzymes reflect the net hepatopathic state resulting from both immunopathic and direct cytopathic mechanisms of HCV, whereas an increase in synthetic function by TPO secondary to thrombocytopenia reflects the immunopathic mechanism of HCV in both patient groups as reported by Hernandez *et al*. [17]. Also, the absence of a correlation between TPO and liver enzymes and a positive correlation between TPO and both albumin and prothrombin concentrations only in cirrhotic patients may be because of the fact that all three are synthesized by the hepatocytes.

The plasma half-life of albumin is 16–24 days [25]; the plasma half-life of prothrombin is 60 h [26]; and the plasma half-life of TPO is 20–40 h [7]. A positive correlation was expected between the TPO level and prothrombin concentration in both groups of patients (CAH and cirrhosis) because of their almost similar half-lives(30 and 60 h, respectively), but we found no significant correlation between TPO and prothrombin concentration in the CAH patient group and a significant correlation between them in the cirrhotic patients. The prothrombin concentration depends not only on the synthetic function of the liver but also on vitamin K, either exogenous or endogenous. However, we found a significant positive correlation between TPO and serum albumin in both groups of chronic liver diseases (CAH and cirrhosis). Serum albumin depends mainly on the synthetic function of the liver.

Surprisingly, we found an insignificant decrease in the TPO level in groups B and C of Child's classification, whereas the TPO level was significantly decreased in group A. Thus, the more severe the degree of cirrhosis, the relatively lower the degree of differences in serum TPO, although the decrease in the TPO level in group B was insignificantly different from that of group A. On the basis of these results, further study of thrombocytopenia and the role of TPO in CLD because of HCV should be studied.

Stimulation of the principal organ of megakaryocytopoiesis, that is the bone marrow, may be the most promising therapeutic intervention for thrombocytopenia in cirrhotic patients. The administration of TPO to patients with liver cirrhosis may help reduce the risk of bleeding in certain situations such as during surgery [3,27]. Thanks to the description of TPO and its modality of action, we now have new insights into the possible treatment options for this stimulation. Thus, putative therapeutic interventions can be divided into two groups: (a) the use of treatment targeted at the TPO receptor (c-Mpl) including synthetic TPOs and TPO-mimetic agents and (b) the use of cytokines with general thrombopoietic potential [3].

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Acknowledgements

Conflicts of interest

All members of internal medicine department in Al-Zahraa University Hospital.

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الملخص العربي

التهاب الكبد الفيروسي (سي) هو السبب الرئيسي لأمراض الكبد المزمنة و تليف الكبد وسرطان الكبد ، فضلا عن أنه أكثر الدواعي شيوعا لزرع الكبد في كثير من البلدان.و قد أجري هذا العمل على أربعين مريضا ثبت أنهم مصابون بمرض الكبد المزمن بسبب فيروس التهاب الكبد الوبائي المزمن سي وتم التحقق من ذلك بإيجابية اختبار وجود الأحسام المضادة للفيروس بالدم ووحود الحامض النووي للفيروس بالدم بتفاعل بي سي ار بالاضافة إلى الموجات الصوتية على البطن وفحص الأنسجة باثولوجيا. وكان عشرون منهم يعانون من التهاب الكبد الوبائي النشط للفيروس سي والعشرون الباقون يعانون من تليف الكبد بسبب الفيروس الكبدي سي. وتضمنت الدراسة أيضا خمسة عشر شخصا سليما ظاهريا ومعمليا كمجموعة ضوابط (تحكم) للمقارنة. جميع المرضى لم تتلق علاج مضاد للفيروسات.وقد تم استبعاد المرضى الذين يعانون من الأسباب الأخرى لأمراض الكبد المزمنة ، وأمراض الكلى المزمنة والسكري واضطرابات الغدد الصماء وأمراض الدم من هذه الدراسه.

وقد خضع جميع الأشخاص لما يلي : التاريخ الطبي الكامل ، الفحص السريري الكامل ، متضمنا الفحوص المختبرية التي شملت صورة الدم كاملة ، واختبارات وظائف الكبد ، وسكر الدم صايم وبعد الافطار بساعتين ووظائف الكليتين و الحمض النووي للفيروس ؛و مستوى الثرومبوبويتين في المصل ، وموجات فوق الصوتية على البطن وخزعة نسيجية من الكبد لفحص الأنسجة وتحديد درجة التليف.

وبينت نتائج الدراسة : انخفاض كبير للغاية في عدد الصفائح الدموية في مرضى التهاب الكبد الوبائي المزمن النشط ومرضى تليف الكبد مقارنة بمجموعة الضوابط . وقد أسفرت النتائج عن زيادة طفيفة ليست ذات دلالة احصائية في مستوى الثرومبوبيوتين بالمصل في حالات الالتهاب الكبدي الفيروسي النشط سي مقارنة بمستواه في الأشخاص الضوابط ، أما بمقارنته بمستواه في حالات التليف الكبدي فهناك زياده ذات دلاله احصائية ، في حين ظهور انخفاض شديد ذو دلالة احصائية في مستوى الثرمبوبيوتين في مصل مرضى التليف الكبدي .

وقد كانت هناك علاقة احصائية ايجابية بين مستوى الثرمبوبيوتين في المصل و عدد الصفائح الدموية في مرضى التليف الكبدي وكذلك علاقة احصائية ايجابية بين مستواه و مستوى الزلال في مصل هؤلاء المرضى. وقد أوضحت نتائج هذه الدراسة أن مستوى الثرمبوبيوتين بالمصل ليس له علاقة بمستوى خمائر الكبد في حالات الالتهاب الكبدي الفيروسي النشط وحالات التليف الكبدي .

هكذا يمكن استنتاج أن زيادة مستوى الثرومبوبيوتين في مصل مرضى الالتهاب الكبدي المزمن النشط للفيروس سي قد يكون استجابة تعويضية بسبب نقص الصفائح الدموية في دم هؤلاء المرضى ولكن مع تقدم المرض و فشل وظيفة الكبد في انتاج هذا البروتين يسبب انخفاض مستوى الثرومبوبيوتين في المصل وبالتالي تسوء حالة نقص الصفائح الدموية في هؤلاء المرضى .

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