British Journal of Medicine & Medical Research
5(7): 864-871, 2015, Article no.BJMMR.2015.093
ISSN: 2231-0614

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Plasma Thrombopoietin Level in Thrombocytopenic Patients with or without Liver Cirrhosis Chronically Infected by the Hepatitis C Virus

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/9860
Editor(s):
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Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=709&id=12&aid=6445

Original Research Article

Received 4th March 2014
Accepted 6th August 2014
Published 10th October 2014

ABSTRACT

Background and Aim: Thrombocytopenia is a frequent problem in patients with post- hepatitis C (HCV) liver cirrhosis and also occurs in chronic HCV-infected patients without liver cirrhosis. The aim of this study was to evaluate the role of plasma thrombopoietin (TPO) in the occurrence of thrombocytopenia in both conditions.
Method: Platelet count and plasma thrombopoietin level and liver function tests were measured in four groups of patients: twenty chronic patients with post-hepatitis C liver cirrhosis and thrombocytopenia (group I), ten chronic HCV-positive patients with liver cirrhosis without

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thrombocytopenia (group II), ten chronic HCV-positive patients without liver cirrhosis with thrombocytopenia (group III) and chronic ten HCV-positive patients without liver cirrhosis and without thrombocytopenia (group IV). Ten normal healthy individuals were included as a control group.

Results: Plasma levels of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), TPO and platelet counts in the four groups of patients were significantly different from their corresponding levels in the control group (P <0.001). There was a significant positive correlation between plasma TPO levels and platelet counts in group III patients (ρ (Spearman's [rho]) = 0.661, P= 0 .038). There was no significant correlation between TPO levels and platelet counts in the other three groups of patients. The logistic regression analysis in the three designated models, using dependent variables (chronic HCV infection, liver cirrhosis and thrombocytopenia) and an independent variable (TPO plasma level) revealed that liver cirrhotic patient and the thrombocytopenic patient have equally the best prediction model for the low plasma TPO.

Conclusion: Decreased thrombopoietin production has a role in the pathogenesis of thrombocytopenia in liver cirrhosis.

Keywords: Thrombopoietin; thrombocytopenia; liver cirrhosis; hepatitis C infection.

1. INTRODUCTION

The glycoprotein thrombopoietin (TPO) is produced at a constant rate, mainly in liver hepatocytes, with only limited extrahepatic production in the kidney, bone marrow and spleen [1]. TPO plays a primary role in the regulation and production of megakaryocytes and platelets [2,3]. TPO and its receptor (Mpl), which regulates megakaryopoiesis, are expressed in the central nervous system, where TPO is thought to exert pro-apoptotic effects on newly generated neurons [4]. The primary target for TPO in bone marrow comprises megakaryocyte progenitors at the late stage of differentiation, such as the colony-forming unit-megakaryocyte (CFU-MK) expressing the fibrinogen receptor [GpIIb/IIIa (Integrin $\alpha_{IIb}\beta_3$)] on platelets of rats [5]. TPO has also been shown to be essential for the full maturation of megakaryocytes [6], but it does not have a direct effect on platelet shedding from mature megakaryocytes [7].

Thrombocytopenia is the presence of a subnormal number of platelets in the circulating blood and is the most common cause of abnormal bleeding [4]. Thrombocytopenia is a common clinical problem in HCV patients. Various studies have consistently shown an increase in platelet counts following successful HCV treatment, thus providing a cause-effect relationship between the two [8,9,10]. Although many therapeutic approaches have been tried to treat HCV-related thrombocytopenia (e.g. interferon dose reductions, oral steroids, intravenous immunoglobulins and splenectomy), the success rates have been shown to be variable and not always reproducible [8]. In patients with cirrhosis, plasma TPO levels have been found to be very low, and this impaired production has been speculated to contribute to the production of thrombocytopenia in this condition [11]. Liver cirrhosis in both humans and animals showed decreased hepatic-TPO production with no evident of compensatory extra-hepatic TPO production [12]. Consequently, there may be other mechanisms, such as humoral and genetic factors, involved in the pathogenesis of thrombocytopenia [13]. Although HCV antibody-positive individuals are almost three times more likely to have a low platelet count than those who are HCV antibody-negative [14], controversy still exists concerning the mechanism of HCV-associated thrombocytopenia. This study aims to evaluate the effect of thrombopoietin (the physiological regulator of thrombopoiesis) on the origin of thrombocytopenia in patients infected by the hepatitis C virus with and without liver cirrhosis.

2. MATERIALS AND METHODS

A total of fifty chronic HCV patients with post-hepatic liver cirrhosis and without liver cirrhosis were recruited for the study, selected from the outpatients of Al Hussien Medical City in the period between November 2011 and December 2012. All subjects underwent detailed clinical and laboratory investigations, including liver function tests.

2.1 Patient Grouping

The patients were grouped as follows:

Group I: Twenty chronic HCV-positive patients with post-hepatitis C liver cirrhosis and thrombocytopenia (10 male and 10 female) with ages ranging from 32 to 59 years (mean ±SE; 44.17±2.36 years).

Group II: Ten chronic HCV-positive patients with post-hepatitis C liver cirrhosis and without thrombocytopenia (4 males and 6 females) with ages ranging from 37 to 61 years (40.39±2.46 years).

Group III: Ten chronic HCV-positive patients without liver cirrhosis and with thrombocytopenia (5 males and 5 females) with ages ranging from 35 to 60 years (46.42±2.77 years).

Group IV: Ten chronic HCV-positive patients without liver cirrhosis and without thrombocytopenia (7 male and 3 female) with ages ranging from38 to 64 years (39.78±2.68 years).

2.2 Control Group

Ten normal healthy persons were included in this study as a control group (5 males and 5 females) with ages ranging from 32 to 54 years (41.35±2.43 years).

Subjects with malignant diseases, renal impairment and acute infections were excluded. The control group subjects had no clinical or laboratory evidence of liver disease. An informed written consent was obtained from each patient and each subject of the control group, and the experiments were conducted according to the ethical forms approved by the University Ethics Committee.

The diagnosis of chronic HCV-positive patients was based on the detection of HCV antibodies using ELISA, quantitative PCR and histopathological findings, in addition to the clinical presentation, radiological and laboratory investigations. Thrombocytopenia was identified when the platelet counts was less than 150 x 10^3/µL. Liver cirrhosis was diagnosed by abdominal sonography which was confirmed by liver biopsy in some cases. Non-cirrhotic chronic HCV-positive patients were recognised by liver biopsy which was taken during the preparation for interferon therapy.

Blood samples were collected from patients and control subjects and each sample was divided into two parts. The first part was used for complete blood count (CBC) within two hours of blood collection. The rest of the specimen was subjected to centrifugation at 3000 rpm for 10 minutes. Plasma was collected for the examination of: (1) liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin] using Hitachi chemistry Autoanalyzer; and (2) Serum TPO concentration using a monoclonal antibody based quantitative sandwich ELISA kit (Quantikine Human TPO Immunoassay, R&D Systems, Minneapolis, MN, USA). All samples were coated with a monoclonal antibody, and washed to remove any unbound antibody. Samples were also treated with an enzyme-linked polyclonal antibody specific for TPO and then washed to remove any excess. A substrate solution was added to all samples producing a colour-related TPO concentration. Finally, the reaction was stopped by adding a stop solution to the specimens. All samples were read at a wavelength of 450 nm and TPO levels were calculated according to the standard curve corresponding to the measured optical density; the results are expressed in pg/ml [15].

2.3 Statistical Analysis

The data obtained were represented as mean± SE. An analysis of Variance (ANOVA) test was used to collectively indicate the presence of any significant difference between several groups. Spearman correlation coefficient (ρ) test was used to describe the association between the different studied parameters. $P<0.05$ was considered statistically significant.

3. RESULTS

The obtained results of liver function tests (ALT, AST and albumin), plasma TPO levels and platelet counts of the four groups of patients and control subjects are shown in (Table 1). Generally, there is a significant difference when comparing the studied variables in the patient groups to their corresponding values in the control subjects. (Fig. 1) illustrates the mean values of TPO levels and platelet counts in the patient groups versus the control group. When comparing the mean values of platelet counts between the patient groups and also between each group of patients and the control group, the data showed a significant difference among all groups ($P<0.001$). On the other hand, TPO levels

showed a significant difference (P<0.001) between patient groups and also between each group of patients and the control group, except between group II and group III (P = 0.362). Meanwhile, comparing ALT and AST between groups, and between groups with control data, revealed a significant difference (P<0.001), except between group II and group III patients (P = 0.511) for ALT, and between group I and group III (P = 0.997) for AST. The levels of plasma albumin in the patients groups and the controls showed no significant differences between group I and group II (P = 1.00), group III and group IV (P = 0.128), and group IV and the control group (P = 0.424), while it was statistically significant between the rest of the patient groups and the controls (P <0.001). Furthermore, the results obtained for TPO levels and platelet counts in each of the patients groups and the control subjects revealed a positive significant correlation in group III patients between the two variables (ρ = 0.661, P = 0 .038) (Fig. 2), while this was not significant in the other three groups of patients (ρ = 0.121, P = 0.612, ρ = 0.442, P = 0.200 and ρ = - 0.37, P = 0.293 in groups I, II and IV, respectively).

For the logistic regression analysis of the obtained data, three models have been designated using the presence / the absence of three parameters as dependent variables (chronic HCV infection, liver cirrhosis and thrombocytopenia) and the plasma level of TPO as an independent variable. The analysis revealed that the patient with liver cirrhosis and the patient with thrombocytopenia have equally the best prediction model for the low plasma TPO. For the two parameters (liver cirrhosis and thrombocytopenia) the Adjusted Odds Ratio (AOR) were [=0.964 (P<0.001) and =0.966 (P<0.001), respectively], while, it was =0.985 (P<0.143) for HCV infected patient as represented in (Tables 2, 3 and 4).

Table 1. Results of plasma liver function tests, platelet counts and plasma TPO levels of the four groups of patients and the control group (mean±SE)

Group	Number	ALT (unit/mL)	AST (unit/mL)	Albumin (gm%)	Platelets (x10^3/ µL)	TPO (pg/mL)
Control	10	15.39±.44	35.22±1.05	4.22±0.17	229.43±1.69	137.38±1.35
Group I	20	51.96±0.56*	58.61±0.74*	2.87±0.07*	69.65±0.75*	60.05±0.47*
Group II	10	57.79±0.68*	63.65±0.41*	2.88±0.096*	192.06±1.49*	158.81±0.45*
Group III	10	59.40±1.666*	58.20±0.68*	3.45±0.12*	91.38±0.61*	161.024±0.47*
Group IV	10	42.59±0.34*	39.26±0.31*	3. 90±0.07*	198.76±0.67*	133.54±0.45*

*=P<0.001

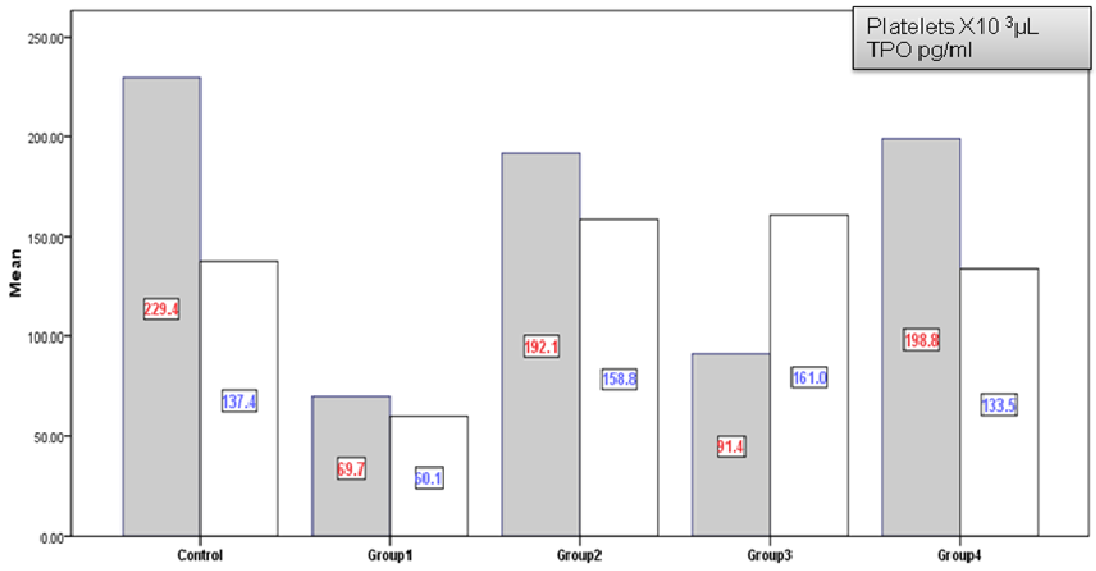

Fig. 1. The relationship between plasma TPO level and platelet counts in patient and control groups

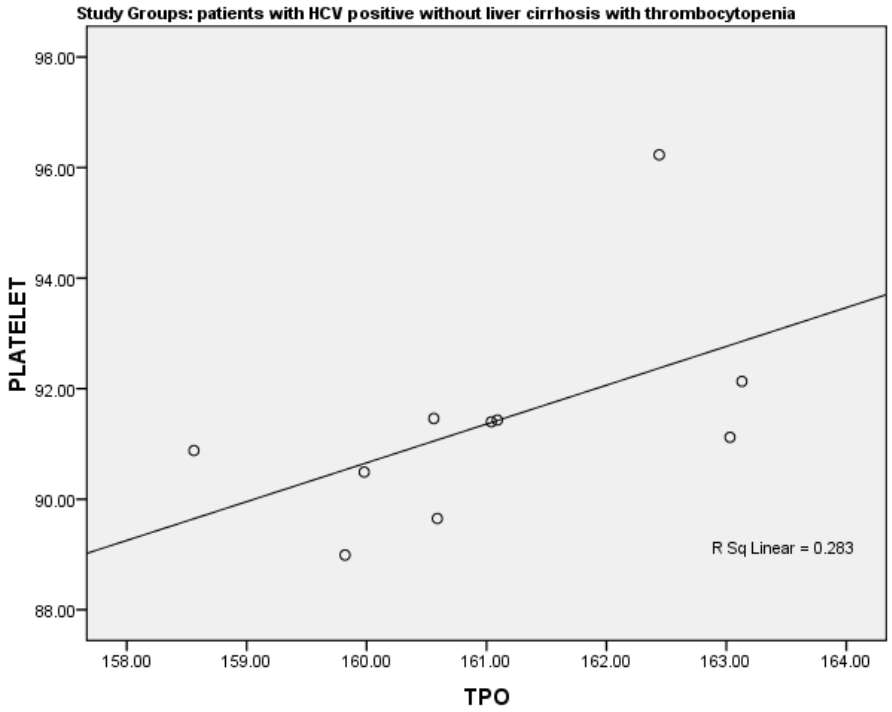

Fig. 2. Correlation between plasma TPO level and platelet counts in group III patients

Table 2. Representing the first model [liver cirrhosis (present/absent)], AOR and significance

Variables in the equation							
1.037		**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**
Step 1[a]	TPO	-.037-	.009	15.039	1	.000	.964

Table 3. Representing the second model [Thrombocytopenia (present/absent)], AOR and significance

Variables in the equation							
1.035		**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**
Step 1[a]	TPO	-.035-	.009	14.762	1	.000	.966

Table 4. Representing the third model [chronic HCV infection (present/absent)], AOR and significance

Variables in the equation							
		B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**
Step 1[a]	TPO	-.015-	.010	2.150	1	.143	.985

a. Variable(s) entered on step 1: TPO; Exp (B) = Adjusted Odds Ratio=AOR

4. DISCUSSION

Thrombocytopenia is a common complication in patients with chronic liver disease that has been observed in up to 76% of patients [14], and moderate thrombocytopenia occurs in approximately 13% of patients with cirrhosis [16]. Thrombocytopenia has a negative impact on the progression of the disease, mainly in the advanced stages, when the platelet count falls

below 50,000/µl [17]. Patients with chronic HCV may present with variable degrees of thrombocytopenia caused by central and/or peripheral mechanisms such as bone marrow suppression, the use of antiviral drugs, a decrease in TPO levels, and anti-platelet antibodies which may develop following platelet destruction due to hypersplenism [17]. In a cross sectional study carried out by Tarantino et al. (2009) [18] to verify the possible involvement of spleen in HCV-related chronic hepatitis, patients showed a significant trend towards increased spleen longitudinal diameter after antiviral therapy, independently of the stage of HCV-related chronic hepatitis [18]. In the absence of hypersplenism or anti-platelet antibodies interactions, the most influential factor on platelet count is the degree of fibrosis in cases of liver cirrhosis and the viral load in cases of liver infection. This was shown in chronic HCV patients in whom alpha-interferon therapy was followed by a significantly increased platelet count as a result of a considerable decrease in the viral load [19]. HCV infection can exert its effects on thrombogenesis via direct suppression of the bone marrow with a reduction of megakaryocyte production, thereby leading to a low level of platelet production [20]. Since over 90% of chronic HCV patients develop high levels of IgG associated with thrombocytes (PAIgG, platelet-associated immunoglobulin G), an autoimmune reaction may lead to mild to moderate thrombocytopenia in liver cirrhosis and contribute to severe thrombocytopenia in cirrhotic patients [21]. Our findings showed that TPO levels are significantly lower in thrombocytopenic patients with liver cirrhosis when compared the level of TPO in both the non-thrombocytopenic group and the control group, which is consistent with the reports of significantly decreased plasma TPO levels in patients with liver cirrhosis [20,22]. However, cirrhotic patients have also shown a significant decrease in plasma TPO levels in contrast to the control subjects and chronic hepatitis C patients [20], which is in agreement with the results obtained by Español et al. [23]; also, our findings showed that there is a significant difference in the levels of plasma TPO in the other three groups of patients to different degrees when compared to the control subjects, which can be explained by the absence of liver cirrhosis and/or the severity of liver cirrhosis.

Li et al. [24] concluded that low TPO production may play a role, along with hypersplenism, in the development of thrombocytopenia in patients with liver cirrhosis. Moreover a correlation between the stage of fibrosis in chronic liver disease patients and their serum TPO levels has been demonstrated [25]. Normal plasma TPO levels exclude any defect in its production, therefore eliminating any role in the aetiology of thrombocytopenia in patients with HCV. However, viral infection of megakaryocytes or any immune reaction could play a role in the production of thrombocytopenia proportional with the TPO levels detected. Many studies have found considerably higher plasma TPO levels in patients with liver disease associated with thrombocytopenia than in control subjects, which might be attributed to the feedback responses of the decreased platelet levels in those patients and expression of their TPO receptors [26]. Our results demonstrated higher levels of plasma TPO in chronic HCV patients without liver cirrhosis and with thrombocytopenia (group III), whereas it was within the normal range in chronic HCV patients without liver cirrhosis and without thrombocytopenia (group VI), suggesting an immune reaction that led to thrombocytopenia in chronic HCV patients without liver cirrhosis rather than being due to the plasma levels of TPO.

A significant correlation was found between the degree of thrombocytopenia and the level of plasma viral load, which supports the findings reported recently by Dai et al. [27]. The correlation between serum TPO level and platelet count was positively significant in the chronic HCV patients without liver cirrhosis but with thrombocytopenia (group III, $\rho = 0.661$, $P = 0.038$; Fig. 2), indicating that the peripheral mechanisms of thrombocytopenia (HCV-mediated autoimmune) play a role here considering that there is no hypersplenism and the patients were not on interferon therapy, which itself can induce bone marrow suppression and, consequently, thrombocytopenia [25]. On the other hand, the plasma TPO levels and platelet counts in the other three groups of patients showed no significant correlation (($\rho = 0.121$, $P = 0.612$, $\rho = 0.442$, $P = 0.200$ and $\rho = -0.37$, $P = 0.293$ in groups I, II and IV, respectively) which may be due to the involvement of more than one mechanism in the production of thrombocytopenia, including the involvement of HCV infection directly or partially in the process. Nevertheless, this does not neglect the important role played by TPO in thrombocytopenia related to chronic liver disease [28]. Furthermore, it had been shown that the successful interferon therapy of patients with chronic hepatitis and thrombocytopenia is accompanied by an improvement in the platelet

count which is mediated by TPO serum levels [29]. Accordingly, it was difficult to establish a stable correlation between TPO levels and platelet count in our study and the levels of TPO cannot be used as an indicator for the severity of the disease, as shown by others [24]. Our results are inconsistent with those previously reported by Koruk et al. [30], who found that thrombocytopenic patients with chronic hepatitis C presented with serum TPO levels similar to those of the healthy control group. Other mechanisms are possibly involved in the development of thrombocytopenia such as peripheral immune-mediated platelet destruction, the presence of anti-TPO antagonists or antibodies and/or a direct viral cytopathic effect on megakaryocytes [31].

5. CONCLUSION

In conclusion, low TPO production may play a role in the development of thrombocytopenia in patients with liver cirrhosis. Normal TPO levels exclude a defect in TPO production as a possible aetiology for thrombocytopenia in patients with chronic hepatitis C viral infection. The mechanism controlling TPO levels and thrombocytopenia may differ in chronic hepatitis C viral infection without cirrhosis. However, an immune mechanism could explain this thrombocytopenia in relation to the detected TPO levels.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kaushansky K. Thrombocytopenia: the primary regulator of megakaryocyte and platelet production. J. Thromb. Haemost. 1995;74:521-525.
2. Kaushansky K. Thrombocytopenia: the primary regulator of platelet production. Blood. 1995;86:419-431.
3. Sungaran R, Markovic B, Chong BH. Localisation and regulation of thrombopoietin mRNA expression in human kidney, liver, bone marrow and spleen using *in situ* hybridisation. Blood 1997;89:101-107.
4. Anna I, Jens W, Juan Z, Olaf H, Matthias B and Christof D. Expression pattern of the thrombopoietin receptor (Mpl) in the murine central nervous system. BMC Dev. Biol. 2010;10:77-89.
5. Kato T, Horie K, Hagiwara T, Maeda E, Tsumura H, et al. GpII/IIIa+ subpopulation of rat megakaryocyte progenitor cells exhibits high responsiveness to human thrombopoietin. Exp. Hematol. 1996;24:1209-1214.
6. Zuker-Franklin D, Kaushansky K. Effect of thrombopoietin on the development of megakaryocytes and platelets: an ultrastructure analysis. Blood. 1996;88: 1632-1638.
7. Horie K, Miyazaki H, Hagiwara T, Tahara E, Matsumoto A, et al. Action of thrombopoietin at the megakaryocyte progenitor level is critical for the subsequent pro-platelet production. Exp. Hematol. 1997;25:169-176.
8. Fazal A, Salman S, Fazal R, Ahmed E, Saeeda Y. Considerations in the management of Hepatitis C virus-related thrombocytopenia with Eltrombopag. Saudi J. Gastroenterol. 2010;16(1):51-56.
9. Danish FA. Current standards in the pharmacotherapy of chronic Hepatitis C and local practices. Infect. Dis. J. 2008;17:93-7
10. Nurden AT, Viallard JF, and Nurden P. New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura. Lancet. 2009;373:1562-9.
11. Martin TG, Somberg KA, Meng YG, Cohen RL, Heid CA, et al. Thrombopoietin levels in patients with cirrhosis before and after orthotopic liver transplantation. Ann. Intern. Med. 1997;127:285-288.
12. Ishikawa T, Ichida T, Matsuda Y, Sugitani S, Sugiyama M, et al. Reduced expression of thrombopoietin is involved in thrombocytopenia in human and rat liver cirrhosis. J. Gastroenterol. Hepatol. 1998;13:907-913
13. Freni MA, Spadaro A, Ajello A, Barbaro E, Scaffidi M, et al. Serum thrombopoietin in chronic liver disease: relation to severity of the disease and spleen size. Hepatogastroenterology. 2002;49:1382-1385.
14. Streiff MB, Mehta S, Thomas DL. Peripheral blood count abnormalities among patients with hepatitis C in USA. Hepatology. 2002;35:947-952.
15. Tahara T, Usuki K, Sato H, Ohashi H, Morita H, et al. A sensitive sandwich ELISA for measuring thrombopoietin in

human serum: serum thrombopoietin levels in healthy volunteers and in patients with haematopoietic disorders. Br. J. Haematol. 1996;3:783-788.
16. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, et al. Thrombocytopenia associated with chronic liver disease. J. Hepatol. 2008;48(6):1000-1007.
17. Peck-Radosavljevic M. Thrombocytopenia in liver disease. Can. J. Gastroenterol. 2000;14(suppl D):D60-D66.
18. Tarantino G, Conca P, Tarantino M, Di Minno MN, Grimaldi E, Chianese D, Riccoio A, Scopacasa F, Capone D. Does spleen volume play a role in patients with HCV-related chronic hepatitis? Int. J. Immunopathol. Pharmacol. 2009;22(4):1009-17.
19. Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. Aliment. Pharmacol. Ther. 2007;26(Suppl 1):13-19.
20. Espanol I, Gallego A, Rabella N, Lerma E, Hernandez A, et al. Thrombocytopenia associated with liver cirrhosis and hepatitis C viral infection: role of thrombopoietin. Hepatogastroenterology. 2000;47:1404-1406
21. Nagamine T, Ohtuka T, Takehara K, Arai T, Takagi H, et al. Thrombocytopenia associated with hepatitis C viral infection. J. Hepatol. 1996;24(2):135-140.
22. Kawasaki T, Takeshita A, Souda K, Kobayashi Y, Kikuyama M, et al. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis. The American Journal of Gastroenterology. 1999;94(7):1918-1922.
23. Español I, Gallego A, Enríquez J, Rabella N, Lerma E, et al. Thrombocytopenia associated with liver cirrhosis and hepatitis C viral infection: role of thrombopoietin. Hepatogastroenterology. 2000;47(35):1404-1406.
24. Li Q, Sun GZ, Wang BE, Jia JD, Ma H, et al. The relationship among the count of platelets, thrombopoietin in patients with liver cirrhosis. Zhonghua Gan Zang Bing Za Zhi. 2004;12(4):210-212.
25. Adinolfi LE, Giordano MG, Andreana A, Tripodi MF, Utili R, et al. Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. Brit. J. Haematol. 2001;113:590-595.
26. Goulis J, Chau TN, Jordan S, Mehta AB, Watkinson A, et al. Thrombopoietin concentrations in patients with cirrhosis and thrombocytopenia and are restored after orthotropic liver transplantation. Gut. 1999 44:754-758.
27. Dai CY, Ho CK, Huang JF, Hsieh MY, Hou NJ, et al. Hepatitis C virus and low platelet count: a study in a hepatitis B & C endemic area in Taiwan. J. Hepatol. 2010;52:160-166.
28. Souza MR, Aguiar LA, Goto JM, Carvente CT, Toledo CF, et al. Thrombopoietin serum levels do not correlate with thrombocytopenia in hepatic schistosomiasis. Liver. 2002;22:127-129.
29. Stanely RG, Ngaiza JR, Atieno E, Jell G, Francklow K, et al. Immune-dependent thrombocytopenia. Clin. Sci. 2003;126(pt3):225-229.
30. Koruk M, Onuk MD, Akcay F and Savas MC. Serum TPO levels in patients with chronic hepatitis and liver cirrhosis and its relationship with circulating thrombocyte counts. Hepatogastroenterology 2002;49:1645-1648.
31. Shiota G, Okubo M, Kawasaki H, Tahara T. Interferon increases serum thrombopoietin in patients with chronic hepatitis C. Br. J. Haematol. 1997;97:340-342.

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