Original Article

Thrombocytopenia and its Related Factors: A Hospital-based, Cross-sectional Study

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Abstract

Introduction: The objective of this study was to explore the association between thrombocytopenia and its related factors. Materials and Methods: This was a hospital-based, cross-sectional study. We retrospectively analysed the medical records of all patients who received periodic health examinations at a medical centre located at Taichung in Taiwan between 2000 and 2004. In all, 5585 subjects were included for further analysis. A complete physical examination, laboratory survey and abdominal ultrasonography were performed on each subject. The *t*-test, chi-square test and multivariate logistic regression analysis were used. Results: The subjects consisted of 3123 men (55.9%) and 2462 women (44.1%). The mean age was 49.4 ± 12.3 years (range, 20 to 87). The overall prevalence of thrombocytopenia was found to be 0.5%, higher in men than in women (0.6% vs 0.4%, *P* = 0.504). After controlling for the other covariates, multivariate logistic regression analysis exhibited that the factors significantly related to thrombocytopenia were increasing age (OR, 1.04; 95% CI, 1.004-1.08), anti-HCV positive (OR, 5.24; 95% CI, 2.08-13.20), liver cirrhosis (OR, 7.93; 95% CI, 2.28-27.62), and splenomegaly (OR, 18.86; 95% CI, 6.86-51.87). Conclusion: It is advisable to further check the hepatic status, if thrombocytopenia is noted.

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Key words: Hepatitis C, Liver cirrhosis, Splenomegaly, Thrombocytopenia

Introduction

Thrombocytopenia is a common clinical problem found in laboratory results during health examinations. Blood platelets play an essential role in haemostasis, thrombosis and coagulation of blood.[1] Platelets are the smallest units of blood cells. They are formed in the bone marrow by the fragmentation of megakaryocyte cytoplasm.[2] The normal platelet concentration in adult ranges from 150,000 to 450,000//μL.[3] They circulate in the blood for 8 to 12 days.[1,2] Bleeding time is generally not prolonged until the platelet count is below 100,000/μL.[4] However, as long as platelet counts are more than 20,000/μL, clinical manifestations may be mild, often limited to easy bruising.[4] If less than 10,000/μL, the risk of spontaneous mucocutaneous bleeding, intracranial haemorrhage or gastrointestinal bleeding increases markedly.[2,4]

A previous study revealed that thrombopoietin, a ligand for the receptor encoded by protooncogene c-mpl, may play an important role in the regulation of megakaryocyte development and platelet production.[5] The production of thrombopoietin is mainly from the liver.[6] In Streiff et al's study, patients with hepatitis C infection are more likely to have low platelet counts.[7] The hepatitis virus principally replicates in the liver and its cardinal manifestation is progression to chronic liver disease. A decreased production of thrombopoietin in patients with chronic liver disease can result in deficient platelet production by the bone marrow.[8,9]

In Taiwan, hepatitis B and hepatitis C infections are hyperendemic, which may lead to liver cirrhosis, and even hepatocellular carcinoma, after many years. We hypothesise a link between the 2 conditions, that patients infected with viral hepatitis may have a higher frequency of thrombocytopenia.

To date, there is little evidence of a relationship between thrombocytopenia and its related factors in Taiwan. This study analysed data collected from a medical centre in Taiwan to explore the following questions: (i) what is the prevalence of thrombocytopenia? (ii) what are the related factors of thrombocytopenia?

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Materials and Methods

This was a hospital-based, cross-sectional study. We retrospectively analysed the medical records of all the subjects who received periodic health examinations with scheduled items at 1 medical centre located at Taichung in Taiwan between 2000 and 2004. In all, 5585 subjects were included for further analysis. The institutional review board of this medical centre approved this study.

Complete physical examinations on the subjects were performed by the doctors at the Department of Family Medicine. If the subjects never smoked or had quit smoking, they were classified as non-smokers. Subjects who currently smoked were classified as smokers. Subjects who never drank alcohol were classified as non-drinkers. Subjects who reported drinking alcohol often were classified as habitual drinkers. Abdominal ultrasonography was performed by the gastroenterologists using a high resolution real-time machine (TOSHIBA Sonolayer SSA-270A, convex-type 3.5 MHz transducer, Tochigi-Ken, Japan).

Body mass index (BMI) was measured as follows: BMI = weight (kg) x height $(m)^2$.

Generalised obesity was defined as BMI ≥27.[10] Venous blood samples were obtained in the morning after a 12-hour overnight fast. Thrombocytopenia was defined as a platelet count of <100,000 platelets/μL.[3] Hepatitis B surface antigen was determined by an enzyme-linked immunosorbent assay (ELISA) (Enzygnost, Dade Behring Marburg GmbH, Germany). Antibody to the hepatitis C virus was determined by EIA test (Abbott HCV EIA, third generation, Abbott Laboratories, Abbott Park, IL).

Statistical analysis on laboratory results was done using the SPSS software (Taiwan Version 10.0, Sinter Information Corp, Taipei, Taiwan). The methods used in the statistical analysis were the *t*-test, chi-square test and the multivariate logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the Study Population

The basic characteristics of the study population are shown in Table 1. Among the 5585 subjects, 3123 were men (55.9%) and 2462 were women (44.1%). The mean age of the subjects was 49.4 ± 12.3 years (range, 20 to 87). The overall prevalence of thrombocytopenia was 0.5%.

Factors Related to Tthrombocytopenia by chi-square test

The association between thrombocytopenia and its related factors by chi-square test are shown in Table 2. The prevalence of thrombocytopenia was higher in men than in women (0.6% vs 0.4%, $P = 0.504$). The factors significantly related to thrombocytopenia were Anti-HCV positive, fatty liver, liver cirrhosis and splenomegaly. Specifically, the following results were obtained for the subjects who were diagnosed with thrombocytopenia: 4.3% of these subjects were anti-HCV positive, 0.3% were not ($P < 0.0001$); 0.2% had a fatty liver, 0.8% did not ($P = 0.002$); 34.6% had liver cirrhosis, 0.4% did not ($P < 0.0001$); and 13.7% had splenomegaly, 0.3% did not ($P < 0.0001$). In addiction, the mean age was 58.5 years for the subjects with thrombocytopenia and was 49.4 years for the subjects without thrombocytopenia ($P = 0.0001$).

Table 1. Characteristics of the Study Population

Variable	No. (%)
Age (mean ± SD), y	49.4 ± 12.3
Sex	
Female	2462 (44.1)
Male	3123 (55.9)
Thrombocytopenia	
No	5556 (99.5)
Yes	29 (0.5)
BMI ≥27	
No	4562 (81.7)
Yes	1023 (18.3)
HBsAg	
Negative	4757 (85.2)
Positive	828 (14.8)
Anti-HCV	
Negative	5308 (95.0)
Positive	277 (5.0)
Fatty liver	
No	3038 (54.4)
Yes	2547 (45.6)
Liver cirrhosis	
No	5559 (99.5)
Yes	26 (0.5)
Splenomegaly	
No	5483 (98.2)
Yes	102 (1.8)
Smoking	
No	4150 (74.3)
Yes	1435 (25.7)
Alcohol consumption	
No	4974 (89.1)
Yes	611 (10.9)

Related Factors of Thrombocytopenia by Logistic Regression

After controlling for the other covariates, multivariate logistic regression analysis showed that the factors significantly related to thrombocytopenia were increasing age, anti-HCV positive, fatty liver, liver cirrhosis and splenomegaly. Specifically, for every 1-year increase in

Table 2. Thrombocytopenia and its Related Factors by the Chi-square Test

Variable	Normal No. (%)	Thrombocytopenia No. (%)	*P*
Age (mean ± SD), y	49.4 ± 12.3	58.5 ± 9.6	0.0001
Sex			0.504
Female	2451 (99.6)	11 (0.4)	
Male	3105 (99.4)	18 (0.6)	
BMI ≥27			0.740
No	4539 (99.5)	23 (0.5)	
Yes	1017 (99.4)	6 (0.6)	
HBsAg			0.157
Negative	4735 (99.5)	22 (0.5)	
Positive	821 (99.2)	7 (0.8)	
Anti-HCV			<0.0001
Negative	5291 (99.7)	17 (0.3)	
Positive	265 (95.7)	12 (4.3)	
Fatty liver			0.002
No	3014 (99.2)	24 (0.8)	
Yes	2542 (99.8)	5 (0.2)	
Liver cirrhosis			<0.0001
No	5539 (99.6)	20 (0.4)	
Yes	17 (65.4)	9 (34.6)	
Splenomegaly			<0.0001
No	5468 (99.7)	15 (0.3)	
Yes	88 (86.3)	14 (13.7)	
Smoking			0.815
No	4129 (99.5)	21 (0.5)	
Yes	1427 (99.4)	8 (0.6)	
Alcohol consumption			0.622
No	4949 (99.5)	25 (0.5)	
Yes	607(99.3)	4 (0.7)	

age, the prevalence of thrombocytopenia increased by 1.04-fold (95% CI, 1.004-1.08; P <0.05); for subjects who were anti-HCV positive, the prevalence increased by 5.24-fold (95% CI, 2.08-13.20; P <0.001); for subjects with liver cirrhosis, the prevalence increased by 7.93-fold (95% CI, 2.28-27.62; P <0.01) and for subjects with splenomegaly, the prevalence increased 18.86-fold (95% CI, 6.86-51.87; P <0.0001). However, the prevalence of thrombocytopenia decreased by 0.33-fold for subjects with fatty liver (95% CI, 0.12-0.93; P <0.05) (Table 3).

Table 3. Related Factors of Thrombocytopenia by Multivariate Logistic Regression

Variable	EP (SE)	OR	95% CI
Intercept	-7.81 (0.99)		
Age (every one year)	0.04 (0.02)	1.04	1.004-1.08*
Anti-HCV positive (yes vs no)	1.66 (0.47)	5.24	2.08-13.20‡
Fatty liver (yes vs no)	-1.11 (0.53)	0.33	0.12-0.93*
Liver cirrhosis (yes vs no)	2.07 (0.64)	7.93	2.28-27.62†
Splenomegaly (yes vs no)	2.94 (0.52)	18.86	6.86-51.87§

95% CI: 95% confidence interval; EP: estimated parameter; OR: odds ratio; SE: standard error;
*P <0.05; †P <0.01; ‡P <0.001; §P <0.0001

Discussion

In general, thrombocytopenia is defined as a condition where there is a subnormal number of platelets in the circulating blood. In our study, thrombocytopenia was specifically defined as platelet count less than 100,000 platelets/μL.[3] A classification of thrombocytopenia based on pathophysiologic criteria includes artificial thrombocytopenia, decreased platelet production, increased platelet destruction and abnormal pooling.[1]

Our study has shown that anti-HCV positive was related to thrombocytopenia, which is compatible with previous studies.[7,11,12] The major clinical consequences of chronic hepatitis C infection are hepatocellular damage, hepatic fibrosis, the progression to cirrhosis with hepatic decompensation, and even the development of hepatocellular carcinoma.[13] A decreased production of thrombopoietin is noted in patients with chronic liver disease.[8,9] In Adinolfi et al's study,[9] advanced hepatic fibrosis, which causes an altered production of thrombopoietin, may play a central role in the pathogenesis of thrombocytopenia in chronic viral hepatitis. A previous study also reveals that interferone-α therapy can increase platelet counts in anti-HCV positive thrombocytopenic patients, which supports the mechanism involving a direct role for hepatitis C virus inhibiting platelet production.[14] Although the real pathogenic mechanism between hepatitis C infection and thrombocytopenia is not well understood, but as mentioned above, may be associated with hepatocellular damage, hepatic fibrosis, liver cirrhosis and inadequate production of thrombopoietin.[8,9,11-13]

In our study, liver cirrhosis was also related to thrombocytopenia. Thrombopoietin, as mentioned before, plays a key role in platelet production and is mainly synthesised in the liver.[5,6] In Koruk et al's study,[15] cirrhotic patients have lower serum thrombopoietin level, and this decreases in level as the degree of cirrhosis progresses. Thus, the impairment of thrombopoietin production may cause the development of thrombocytopenia in an advanced stage of liver disease.[15]

In our study, splenomegaly was also related to thrombocytopenia. Splenomegaly is a common feature in patients with chronic liver disease. It is usually asymptomatic but may cause hypersplenism.[16] The spleen normally

contains approximately one-third of the total platelet mass, leaving the remaining two-thirds evenly distributed in the circulation.[17] In normal subjects, approximately 37% of platelets are sequestered in the spleen and 24% in the liver. These figures in patients with splenomegaly are 71% in the spleen and 14% in the liver.[18] In Akyüz et al's study,[19] the spleen size is inversely correlated with the platelet count. The survival time of platelet increases 47% after splenectomy.[1] Thus, splenic sequestration due to splenomegaly is one of the main factors for the thrombocytopenia.[18,19]

Our study also showed that for every 1-year increase in age, the prevalence of thrombocytopenia increased by 1.04-fold. In Wang et al's study,[11] older persons (≥65 years of age) are 4 times more likely than those in other age groups to have thrombocytopenia. In our study, the prevalence rates of anti-HCV positive were 1.4% in the 20 to 39 years age group, 5.0% in the 40 to 64 years age group, and 11% in the ≥65 years age group (not shown in table). We believe long-term exposure to hepatitis C infection may partially explain this increased relative risk. On the other hand, whether the increase in the prevalence of thrombocytopenia with age is due to the higher incidence of myelodysplasia, predominantly occurring in older patients, also needs further evaluation.

In our study, fatty liver was inversely related to thrombocytopenia. In Wang et al's study,[11] 5.1% of the anti-HCV-positive participants with fatty liver and 2.3% of those with normal liver sonographic findings has thrombocytopenia. To date, little is known about the real biologic basis of the association between fatty liver and thrombocytopenia. We cannot make any expanded explanation as to why fatty liver is inversely related to thrombocytopenia.

There were several limitations in our study. Firstly, we did not have data for blood films. Therefore, possible causes of thrombocytopenia due to marrow diseases, either primary or secondary, could not be well evaluated. Secondly, the anti-coagulant edetic acid (EDTA), which is used for routine blood counts, may cause platelet agglutination. This occurs in about 1 per 1000 persons, irrespective of the presence or absence of any disease.[2] Thirdly, we did not consider the other causes of thrombocytopenia, such as drug-induced thrombocytopenia.[2,20-21]

Conclusion

The pathogenesis of thrombocytopenia is multi-factorial. In this current study, increasing age, anti-HCV positive, liver cirrhosis and splenomegaly are found to be the factors significantly related to thrombocytopenia. It is therefore advisable to further check the hepatic status if thrombocytopenia is present.

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