Comparison of Platelet Count Reduction in Patients awaiting Liver Transplantation with and without Primary Sclerosing Cholangitis: A Cohort Study

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Abstract

Background: Thrombocytopenia is the most well-known hematological abnormality occurring in patients with liver cirrhosis. However, the rate of platelet count reduction is not the same across different chronic liver disease etiologies. Therefore, the aim of the present study was to compare the differences in the platelet count levels between primary sclerosing cholangitis-related cirrhosis (PSC-C) and other causes of liver disease.

Methods: In this cohort study, the association between PSC-C and risk of platelet count reduction was investigated. The platelet counts were repeatedly measured among 242 consecutive cirrhotic patients (144 males and 98 females) including 67 patients with PSC-C and 175 patients with non-PSC-C who were on the waiting list for liver transplantation. The Poisson regression analysis was used to assess the relationship between platelet count reduction and PSC-C, after adjusting for potential confounding factors.

Results: During the five years of follow-up, comparison between the two groups revealed that significantly higher levels of platelet were found in PSC-C patients when compared to the non-PSC-C group [148 (106–280) (×10^9/µL) vs. 79 (50–110) (×10^9/µL), respectively, \( P < 0.001 \)]. After adjusting for confounding factors, a significant association was observed between non-PSC-C and the risk of platelet count reduction (relative risk, RR: 14.81, 95% CI: 1.21–160.42; \( P = 0.03 \).

Conclusion: The findings indicate that PSC-C patients present with mild degrees of thrombocytopenia compared to other causes of chronic liver disease.

Keywords: Liver cirrhosis, Liver transplantation, Primary sclerosing cholangitis, Thrombocytopenia

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Introduction

Liver cirrhosis (LC) is the result of diffuse processes of liver cell necrosis, replacement by extensive fibrosis, liver cell regeneration and subsequent development of regenerative nodules.1 Patients with LC, regardless of their etiology, develop changes in their hemostatic parameters including decreased levels of platelet counts.2,3 Thrombocytopenia is defined as a platelet count less than 150×10^9/µL, and occurs in 6%–84% of patients with LC.4,5 Various theories have been proposed regarding the causes of thrombocytopenia in cirrhotic patients such as reduced levels of thrombopoietin, sequestration of platelets in the spleen due to portal hypertension, destruction of platelets as a result of autoantibodies and secondary bone marrow suppression due to underlying liver disease.6–9 Although thrombocytopenia is believed to be an indicator of advanced liver disease, it has also been used as a marker of prognosis.10 However, the rate of platelet count reduction appears to be different among various etiologies of liver disease.19

Primary sclerosing cholangitis (PSC) refers to a heterogeneous, rare, cholestatic liver disorder with unknown underlying pathogenesis.20,21 Despite increased knowledge regarding certain aspects of PSC, the exact pathophysiology of its progression to cirrhosis remains largely unknown. Currently, there are no established laboratory tests for differentiating PSC from other causes of LC and its diagnosis often requires a multidisciplinary approach.22 Several studies have indicated that patients with PSC often show distinct laboratory features such as a hypercoagulable state seen in cholestatic liver disease rather than non-cholestatic etiologies.23,24 However, these studies have not assessed platelet count differences between PSC and non-PSC etiologies.

Given the diverse nature of platelet count changes in different liver disease etiologies, and since there was no large study regarding platelet count changes in patients with a diagnosis of PSC-related cirrhosis (PSC-C), we...
conducted this observation among LC patients (PSC-C and non-PSC-C) who were on the liver transplantation waiting list.

Materials and Methods
Patient Population
The present cohort study was performed on all consecutive cirrhotic patients who were on the waiting list for liver transplantation in a liver transplantation program (affiliated to Tehran University of Medical Sciences, a tertiary referral center for chronic liver disease) from March 2013 to January 2017. Data regarding patients' demographic, clinical and hematological characteristics were obtained. The diagnosis of PSC was made after the exclusion of a variety of other causes of cholestatic liver disease and secondary sclerosing cholangitis, as well as the combination of prolonged cholestasis and imaging modalities of magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography indicating the presence of bile duct changes with multifocal strictures and “beaded” appearance.20,25,26 According to the European Association for the Study of the Liver guidelines, the diagnosis of other cirrhosis etiologies was established.27 Patients with a prior history of splenectomy, incomplete hematologic assessment, cholangiocarcinoma, recent cholangitis, use of any medications that might influence the platelet counts (Interferon, Azathioprine, Cellcept), or those who received platelet transfusion before enrollment were excluded from the study. The severity of LC was assessed using Child–Pugh and Model for End-Stage Liver Disease (MELD) scores. The study protocol was approved by the ethics committee of Tehran University of Medical Science. Informed consent was obtained from all included patients. The study was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.28

Measurements
Repeated measurements of standard routine laboratory tests including white-blood cell count (WBC), and hemoglobin, platelets, creatinine, international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and erythrocyte sedimentation rate (ESR) were collected. Platelet count was measured in EDTA-treated blood samples collected in 2–3 h, using Sysmex's unique fluorescence flow cytometry (the results was confirmed by double-checking or using the peripheral blood smear for each analysis).

Patients were divided into four groups based on the MELD score quartiles: 1) MELD score <12; 2) MELD score 12–15; 3) MELD score 15–20; and 4) MELD score >20. Spleen size was evaluated based on ultrasonography, and its largest diameter was classified into three groups (group 1: <120 mm, group 2: 120–150 mm, group 3: >150 mm). Portal vein size was determined either by CT scan or ultrasonography, and categorized into three groups according to the mean diameter of the portal size (12, 12–14 and >14 mm). Esophageal variceal (EV) grading was assessed based on the Japanese classification including: F0 (no EV detected), F1 (small or less than 5 mm straight EV), F2 (slightly enlarged tortuous EV occupying less than one-third of the esophageal lumen) and F3 (large coil-shaped EV that occupied more than one-third of the esophageal lumen).29

Statistical Analysis
Nominal and ordinal variables were reported as count (%), and continuous numeric variables were reported as mean ± standard deviation (SD) or the median and 25th and 75th percentiles if non-normally distributed. We estimated whether data were distributed normally using Kolmogorov–Smirnov and Shapiro–Wilks tests, as well as Q-Q plot. Parametric and non-parametric analyses were used according to the finding of these tests. Pearson correlation was used for normally distributed data and Spearman rank correlation was used for non-normally distributed data. Data on the diagnosis of PSC vs non-PSC, as well as platelet counts and other hematologic parameters including age, sex, and MELD score, were available for all patients. Five percent of the population did not have data on EV bleeding, 8% did not have data on diuretic intake, and 9% did not have data on hepatic encephalopathy.

The incidence of different levels of decreased platelet count was calculated for the PSC-C and non-PSC-C groups. With the sample size of the present study, at a significance level of 5%, we were able to detect a difference in platelet counts of at least 10% with 99% power. Poisson regression analysis was performed in order to test the association between platelet count reduction and diagnosis of PSC-C by calculating the relative risk (RR) and 95% confidence interval (CI). The goodness-of-fit of the model was assessed by Hosmer–Lemeshow test. A directed acyclic graph was used to assist in the selection of appropriate covariates (confounder and competing exposure) by modeling the relationships between potential covariates, PSC state and platelet count reduction (Figure S1, see Supplementary file 1). Confounding factors including gender, age, WBC, ESR, cholesterol, MELD score, portal size and spleen size were included as covariates in the multivariable models. These variables were included given that they were individually significantly associated with both platelet count and diagnosis of PSC. Statistical significance was defined as $P < 0.05$. Data were analyzed using SPSS 23.0 (SPSS Inc.; Chicago, IL).

Results
Characteristics of Patients
A total of 242 cirrhotic patients were included in this
study. Table 1 describes the baseline demographic and biochemical data. The mean age of patients was 37.2 ± 14.1 and 42.1 ± 14.2 years for patients with PSC-C and non-PSC-C, respectively. The most common etiology of LC in this study was PSC which was found in 67 patients (27.6%) followed by cryptogenic (23.1%), Hepatitis B (16.5%), autoimmune hepatitis (12.8%), Hepatitis C (8.7%), Wilson (4.1%) and primary biliary cirrhosis (2.5%). Compared to non-PSC-C patients, the PSC-C patients were younger (P = 0.016). In both groups, no significant difference was found in mean age between males and females (P = 0.2). The MELD score was similar in both groups (PSC-C, 15.6 ± 4.2 vs. non-PSC-C, 16.7 ± 5.7).

### Table 1. Baseline Characteristics of 242 Cirrhotic Patients

| Demographics | PSC-C (n = 67) | Non-PSC-C (n = 175) | Total | P       |
|--------------|---------------|---------------------|-------|---------|
| Age (year) (±SD) | 37.40 ± 13.81 | 42.12 ± 14.22       | 40.81 ± 14.24 | 0.02*   |
| Gender | | | | 0.41 |
| Male (%) | 37 (55.2) | 107 (61.1) | 144 (59.9) | 0.13 |
| Female (%) | 30 (44.8) | 68 (38.9) | 98 (40.5) | 0.85 |
| Platelet (×10^3/µL) (IQR) | 148 (174) | 79 (60) | 91 (74) | 0.001** |
| WBC (/mm^3) (IQR) | 4200 (1800) | 3000 (1300) | 3500 (2300) | 0.001** |
| Hb (g/dL) | 10.56 ± 1.85 | 11.29 ± 1.85 | 11.10 ± 1.88 | 0.007* |
| ESR (mm/h) (IQR) | 10.56 ± 1.85 | 11.29 ± 1.85 | 11.10 ± 1.88 | 0.007** |
| MCV | 87.53 ± 12.26 | 88.21 ± 13.67 | 88.03 ± 12.03 | 0.683* |
| MCV > 95 (%) | 38.5 | 32 | 31.7 | 0.016* |
| INR (IQR) | 1.4 (0.4) | 1.7 (0.3) | 1.6 (0.5) | 0.001** |
| Ferritin (IQR) | 50.5 (83.4) | 61.5 (136.4) | 54 (124) | 0.247 |
| Cholesterol (mg/dL) | 183.01 ± 74.84 | 141.47 ± 34.79 | 152.75 ± 52.18 | 0.001* |
| LDL (mg/dL) | 114.26 ± 58.76 | 78.10 ± 27.56 | 89.35 ± 33.16 | 0.001** |
| HDL (mg/dL) | 90 (74.2) | 70 (39.3) | 81.4 (42.7) | 0.008** |
| Albumin (g/dL) | 41.35 ± 20.21 | 43.78 ± 14.90 | 43.04 ± 16.70 | 0.442* |
| Creatinine (mg/dL) (IQR) | 3.37 ± 0.57 | 3.43 ± 0.59 | 3.42 ± 0.59 | 0.473* |
| Total bilirubin (mg/dL) (IQR) | 8.02 (10.2) | 2.5 (2) | 2.8 (3.5) | 0.001** |
| Portal size diameter (mm) | 12.68 ± 3.07 | 13.58 ± 3.09 | 13.33 ± 3.00 | 0.081* |
| Spleen size (mm) | 165.45 ± 41.28 | 156.61 ± 37.47 | 158.94 ± 38.61 | 0.146* |
| Esophageal varices (%) | | | | |
| F0 | 13 (26.5) | 14 (2.8) | 27 (13.4) | 0.007** |
| F1 | 11 (22.4) | 48 (31.4) | 59 (29.2) | 0.007** |
| F2 | 16 (32.7) | 42 (27.5) | 58 (28.7) | 0.007** |
| F3 | 9 (18.4) | 49 (32) | 58 (28.7) | 0.007** |
| MELD | 16.7 ± 5.7 | 15.6 ± 4.2 | 15.58 ± 5.10 | 0.021** |
| Child-Pugh (IQR) | 9 (3) | 8 (2) | 8 (3) | 0.25* |
| Esophageal variceal bleeding (%) | 16 (23.8) | 55 (31.4) | 71 (29.3) | 0.348 |
| Diuretic intake H. (%) | 18 (23.8) | 55 (31.4) | 73 (30.1) | 0.910 |
| SBP Hx. (%) | 1.5 | 5.1 | 3 | 0.2 |
| Hepatic encephalopathy Hx. (%) | 38 (56.7) | 100 (57.1) | 138 (57) | 0.103 |
| IBD Hx. (%) | 43 (64.1) | 100 (57.1) | 138 (57) | 0.103 |
| Colectomy Hx. (%) | 15 (22.3) | 100 (57.1) | 138 (57) | 0.103 |
| PVT Hx. (%) | 3 (4.4) | 12 (6.8) | 15 (6.1) | 0.610 |
| Comorbid disease (%) | 5 (3.3) | 25 (28.1) | 30 (28.8) | 0.678 |

Data are presented as Mean ± SD. IQR: Inter quartile range with 75th and 25th percentiles.

PSC-C: Primary sclerosing cholangitis related cirrhosis; WBC: white blood cell; Hb: hemoglobin; ESR: Erythrocyte sedimentation rate; MCV: Mean corpuscular volume; LDL: Low-density lipoprotein; TG, Triglycerides; HDL: High-density lipoprotein; MELD, Model for end stage liver disease; UTI, Urinary tract infection; PVT, portal vein thrombosis; SBP, Spontaneous bacterial peritonitis.

*Between-group comparison was made using Mann–Whitney’s U test.

**Between-group comparison was made using independent t test.
Table 2. Multivariable Poisson Regression Analysis on the Association Between Non-PSC-C and Risk of Platelet Count Reduction

| Covariates          | RR   | 95% CI       | P     |
|---------------------|------|--------------|-------|
| Non-PSC-C diagnosis | 14.81| 1.21–160.42  | 0.03  |
| Age                 | 1.009| 0.86–1.07    | 0.38  |
| WBC (/mm³)          | 0.98 | 0.97–1.00    | 0.02  |
| Cholesterol (mg/dL) | 1.002| 0.98–1.01    | 0.31  |
| Portal size (mm)    | 1.11 | 0.66–1.75    | 0.31  |
| Spleen size (mm)    | 1.009| 0.98–1.03    | 0.35  |

PSC-C, Primary sclerosing cholangitis related cirrhosis; WBC, White blood cell; RR, relative risk; CI, confidence interval.

Comparison of Platelet Count in Different Spleen Size Categories
The results of comparing platelet counts between PSC-C and non-PSC-C across different spleen size categories indicated that in all spleen groups, there were higher platelet counts in PSC-C than non-PSC-C (P < 0.001) (Figure 2C). In both PSC-C and non-PSC-C groups, a significant negative correlation existed between platelet counts and spleen size (r = -0.43, P = 0.001 vs r = -0.34, P < 0.001).

Discussion
In the present study, we evaluated patients’ platelets counts in relation to the spectrum of chronic liver disease etiologies. Our findings revealed that the platelet count reduction was significantly higher in cirrhotic patients with non-PSC-C when compared to patients with a
diagnosis of PSC.

Coagulation disorders are closely linked to progressive liver failure and account for adverse outcomes among cirrhotic patients. Several studies have shown that the degree of thrombocytopenia is different in various chronic liver disease. Tejima et al. reported that patients with hepatitis C-related hepatocellular carcinoma and advanced LC had worsening degrees of thrombocytopenia compared to those with hepatitis B-related hepatocellular carcinoma. They suggested that the underlying mechanism for the greater levels of thrombocytopenia in patients with hepatitis C-related cirrhosis may be due to impaired platelet production rather than platelet destruction. Another study demonstrated that patients with hepatitis C-related cirrhosis had significantly lower platelet counts compared to cirrhotic patients with non-alcoholic fatty liver disease etiology. In the current study, we found significantly higher levels of platelet count in PSC-C patients compared to other cirrhotic etiologies. To the best of our knowledge, this is the first study to delineate the platelet count differences between patients with PSC-C and non-PSC-C diagnosis.

Previous studies have shown that bleeding complications in patients with advanced PSC are much less frequent.
limited.

Our findings in the present study are in accordance with previous reports, which may provide new insight about the involvement of platelets in the pathogenesis of liver disease progression and fibrosis in PSC. Although we were unable to precisely explain the pathophysiologic background of increased levels of platelet count in PSC-C patients, several potential explanations for this finding could be mentioned.

Previous studies show that an increase in fibrinogen is well established as a causative factor for increasing ESR. Moreover, higher levels of fibrinogen have been previously described in cholestatic liver disease compared to other liver diseases. Therefore, elevated fibrinogen levels are associated with stable platelet counts in cirrhotic PSC patients and result in decreased platelet destruction. Another reason could be the increased levels of inflammatory markers such as ESR and CRP in PSC-C patients compared to patients with viral or alcoholic and non-alcoholic liver disease, which may lead to higher levels of platelets in PSC-C patients. The relationship between increased platelet counts and inflammatory disease have been also shown in other medical conditions.

Although we did not measure fibrinogen levels in our survey, the levels of inflammatory markers such as ESR were significantly higher among PSC-C patients compared to non-PSC-C etiologies and this in turn may explain the reason for higher platelet counts in our PSC-C patients. The underlying reason for this discrepancy is unclear. PSC is a disease with recurrent cholangitis and it might be possible that inflammatory processes in the cholangitis events could play a major role in intervening different stages of thrombopoiesis and affecting platelet levels. In addition, it has been assumed that there is better preservation of parenchymal tissue in the less involved area of the liver in PSC. This fact could be due to the non-uniform nature of biliary stricture and beading in PSC, which subsequently results in higher levels of coagulation factors, as well as platelet counts in PSC-C patients.

Given the complex nature of PSC and lack of clear-cut diagnostic criteria, establishing a precise diagnosis of PSC is still problematic. Diagnosis of PSC is usually based on evidence of a cholestatic pattern of liver biochemistries in combination with typical imaging findings. Liver biopsy findings are not completely supportive of diagnosis, confirmation and staging of PSC. However, due to the invasive nature of liver biopsy, sampling error and high costs, the application of this procedure has been limited. Currently, the use of non-invasive diagnostic methodologies have been proposed, including serum-based markers or models in the assessment of prognosis of cirrhotic patients in various kinds of liver diseases. However, limited data exists regarding noninvasive diagnostic tests in terms of distinguishing between PSC-C and other cholestatic cirrhosis etiologies.

On the other hand, it should be noted that the findings presented in this study indicate the inability of predicting the severity of hepatic fibrosis among PSC patients based on the platelet-dependent models such as aspartate aminotransferase-to-platelet ratio index, gamma-glutamyl transferase-to-platelet ratio, fibrosis index based on the 4 factors, and red blood cell distribution width-to-platelet ratio. Therefore, in the PSC-C patients, this context of platelet count status should be considered in the application of models predicting progression to cirrhosis.

Recently, in a large cohort of PSC patients from the United Kingdom (UK-PSC score), a new risk scoring model was developed in order to predict the outcome of patients diagnosed with PSC. They concluded that platelet counts along with other parameters such as bilirubin, albumin, hemoglobin, alkaline phosphatase, variceal bleeding and cholangiographic disease distribution have a better performance in risk assessment of PSC patients when compared to previous models. Future larger studies are needed to validate these models for assessment of progression of liver disease among PSC-C patients.

The present study had several limitations. First, the relatively small sample size of our study may have reduced the power to detect a significant correlation between platelet counts and PSC diagnosis. Second, we did not have an exact assessment of liver fibrosis and portal hypertension of study subjects by histology review and hepatic venous pressure gradient. Third, the wide range of the confidence interval of the relative risk of non-PSC-C diagnosis could be due to the possibility of sparse-data bias as previously described. Therefore, the results of the present study should be interpreted in the context of its limitations.

In summary, the findings of this cohort indicate that PSC-C patients presented with mild degrees of thrombocytopenia compared to other causes of liver disease. The reason for this discrepancy is unknown. Further studies are warranted to clarify the exact molecular mechanism and possible clinical implications of this finding in management of patients with PSC-C awaiting liver transplantation.

**Authors’ Contribution**

MNT (Critical revision of the manuscript, Study concept and design), BM (Acquisition, analysis and interpretation of data, drafting of the manuscript), AE, FAA, HJH (participated in the data acquisition), MK (analysis, interpretation of data, statistical analysis), and AJ (Study concept and design, critical revision of the manuscript).

**Conflict of Interest Disclosures**

The authors have no conflict of interest to declare.
Ethical Statement
The study protocol was approved by the ethics committee of Tehran University of Medical Science. Informed consent was obtained from all included patients. The study was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.

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Supplementary Materials
Supplementary file 1 contains Figure S1.

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