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Factors Associated with the Platelet Count in Patients with Chronic Hepatitis C

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Abstract

Background—There are many potential causes of thrombocytopenia in patients with chronic hepatitis C (CHC).

Aims—We sought to determine the association between thrombopoietin (TPO) level, immature platelet fraction (IPF), immunoglobulin G (IgG) level, spleen size, and the platelet count in CHC.

Methods—We studied a consecutive sample of patients enrolled in an observational study at a referral-based research center, excluding subjects based on eligibility criteria. TPO, glycocalicin, and von Willebrand Factor (vWF) levels were determined using stored sera. Hepatic fibrosis was assessed via transient elastography (TE) when available, and clinical laboratory values and radiologic data were obtained from the medical record. We performed analyses of the relationships between independent variables and the platelet count.

Results—On univariate analysis, the following variables were significantly associated with the platelet count: age, alanine aminotransferase (ALT), direct bilirubin, total bilirubin, IPF, international normalized ratio (INR), spleen size, vWF, glycocalicin, fibrosis stage on liver biopsy, and TE (P-values all <0.05). A multivariable model determined that imputed TE score, TPO, IPF, and spleen size were independently associated with the platelet count (P-values all < 0.05).

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Author contributions: MMT coordinated the project, XZ performed the statistical analysis, AB, MSM, and SP performed the ELISAs, TT reviewed charts for exclusion criteria, ER helped obtain transient elastography data, DEK performed platelet staining on biopsies, TH supervised.

Conflicts of interest: None.

Conclusions—The platelet count in CHC is significantly associated with fibrosis, TPO level, IPF, and spleen size. Our findings challenge the proposed mechanism of decreased TPO levels or decreased bone marrow production of platelets as a cause of thrombocytopenia in CHC. Future studies focusing on the effects of fibrosis and splenomegaly on platelets may shed more light on the pathophysiology of thrombocytopenia in patients with CHC.

Keywords

platelet biology; non-invasive markers; conceptual model

INTRODUCTION

Thrombocytopenia is a common problem in patients with chronic liver disease, and is associated with increased bleeding complications, longer hospital stays, and higher costs.[1] Data from National Health and Nutrition Examination Surveys (NHANES) demonstrated a prevalence of thrombocytopenia of 7.6% among hepatitis C virus (HCV)-infected individuals.[2] A systematic review on thrombocytopenia in patients with chronic hepatitis C (CHC) found that more than half of the selected studies reported the prevalence of thrombocytopenia in patients with HCV to be 24% or higher.[3] Most studies on the pathophysiology of thrombocytopenia in chronic hepatitis C have focused on patients with cirrhosis, but there is evidence that platelet counts steadily decline with earlier stages of fibrosis.[4] Clinicians frequently use the platelet count as an indicator of disease stage and the platelet count is included in many noninvasive assessments of fibrosis, such as the aspartate aminotransferase-to-platelet ratio index (APRI) and FIB-4.[5–7] Similarly, the platelet count has been used along with spleen size and transient elastography to identify patients with clinically significant portal hypertension.[8]

Mechanisms thought to contribute to thrombocytopenia include decreased production, splenic sequestration, endothelial dysfunction, and autoimmune destruction.[9–11] Thrombopoietin (TPO) is a growth factor produced by the liver that stimulates development of the megakaryocytic line in the bone marrow and has been found to decline with advancing HCV-related liver disease.[12–14] The immature platelet fraction is a relatively new laboratory test that measures the earliest form of platelets in the periphery—reticulated platelets.[15] Immunoglobulins are believed to opsonize platelets that are then destroyed in the spleen.[16] Hypersplenism is often implicated in thrombocytopenia in the cirrhotic or portal hypertensive patient.[17] Other factors that may influence the platelet count in CHC patients include platelet-associated antibodies and antiplatelet immunoglobulins. An autoimmune thrombocytopenia associated with HCV has been described, and antiplatelet antibodies might be involved. However, previous reports of CHC patients have found that the presence of antiplatelet antibodies did not affect the platelet count.[18] Vascular endothelial dysfunction has also been found to play a role in thrombocytopenia in patients with CHC. Namely, von Willebrand Factor (vWF) and thrombomodulin have been found to be significantly correlated with the platelet count in patients with CHC.[10] Plasma glycocalicin is a fragment of GPIbα on platelet membranes and has been reported to be elevated in patients with cirrhosis.[19] Prior studies have not found significant correlation between D-dimer,

plasminogen activator inhibitor-1 (PAI-1), or C-reactive protein (CRP) and the platelet count in patients with chronic HCV.[10]

Many factors influence the platelet count in patients with CHC, but the etiology of thrombocytopenia in this patient population is incompletely understood.[19–21] Although the platelet count has proven useful for predicting fibrosis and esophageal varices, there are clinical scenarios where the degree of thrombocytopenia belies the stage of fibrosis.[22–24] A better understanding of the factors involved and their relative contributions may lead to better management, novel therapeutics, and improved clinical outcomes for patients with chronic liver disease. In this cross-sectional study, we sought to assess the contribution of various factors to the platelet count in patients with CHC and to determine the contribution of other as yet unknown factors (Figure 1).

MATERIALS AND METHODS

This was a retrospective, cross-sectional analysis of patients who gave informed consent to participate in an observational protocol that longitudinally follows patients with various types of liver disease. The protocol was approved by the NIH/NIDDK Institutional Review Board, in accordance with the Helsinki Declaration of 1975. All patients are screened for HIV prior to enrollment in the protocol, and patients with excessive alcohol use are not enrolled. Patients are seen regularly in the hepatology clinic, and clinical assessments, laboratory data, radiology data, patient reported outcome data, and serum samples are collected on a routine basis.

We selected a consecutive sample of patients meeting the following criteria: a) a diagnosis of CHC, b) laboratory results of interest and stored serum at a given time point, c) imaging of the spleen within one year of the chosen time point, and d) no medications, toxins, comorbidities known to affect platelet count within six months of the chosen time point. Patients with CHC by definition had detectable HCV RNA in their serum. Patients with any stage of fibrosis were eligible. All medications taken by the patient at the time of serum storage per the medical record were reviewed in determining eligibility. Medications that prompted exclusion were peginterferon, ribavirin, warfarin, and imatinib. Furthermore, all patients were interferon-naïve at the time study serum was collected. Toxins considered in the eligibility process included excessive alcohol use (>2 standard drinks/day in men, > 1 standard drink/day in women) and any illicit drug use. Comorbidities prompting exclusion were splenectomy, sickle cell disease, HIV, and malignancies.

The measures obtained for each patient were: a) clinical labs, including ALT, INR, quantitative immunoglobulins, immature platelet fraction, platelets, b) thrombopoietin, glycocalicin, and vWF measured on stored sera, c) spleen length in centimeters as determined by ultrasound, and d) fibrosis on biopsy or TE within three years of the chosen time point, when available. The immature platelet fraction based on RNA content was determined using an automated counter as previously described.[25]

The NIH Biomedical Translational Research Information System (BTRIS) was used to determine a cohort meeting the study criteria. It was also used to retrospectively glean

demographic, laboratory, radiology, and pathology data from the electronic medical record system.

All sera were stored at −80° C in 2009 or later, with minimal freeze-thaw cycles. Enzyme-linked immunosorbent assay (ELISA) was performed for TPO (R&D Systems, Minnesota), glycocalicin (USCN, China), and vWF (Abcam, Massachusetts). The effect of time on assay results was checked.

TE was measured with the FibroScan (Echosens, France) within three years of the date of laboratory values. The standard (M) probe or extra-large (XL) probe was used according to patient habitus, under examining conditions recommended by the manufacturer. Ten valid measurements were required in order to generate a result. TE results in kilopascals (kPa) were expressed as the median of all valid measurements.

Because TE data were available for only a portion of the cohort, a separate multivariable regression model to predict TE scores was developed and used to impute values for missing data. The predictors in this model of TE were: age, body mass index (BMI), ALT, AST, total bilirubin, alpha-fetoprotein (AFP), gamma-glutamyl transferase (GGT), and steatosis assessed via ultrasound.

Liver biopsies from a subset of the patients with Ishak fibrosis scores of either 0–1 or 5–6 were stained for P-selectin (CD62P), a platelet marker.

We performed univariate and multivariable analyses to find factors that are associated with the platelet count. The primary factor variables of interest we investigated were: TPO, IgG, immature platelet fraction, and spleen size. Other candidate factors were: race, ALT, INR, glycocalicin, vWF, and TE score. We estimated slope coefficients for each factor with respect to a given change in the platelet count when considering the entire sample. We also calculated the R^2 of the model predicting platelet count.

A sample size of 102 patients was determined, based on an analysis involving multiple comparisons and used a Bonferroni correction for four major predictor variables, with an initial α of 0.05 and β of 0.2. The statistical test used to calculate the sample size was a simple linear regression between spleen size and platelet count, and a sample size of 102 would allow us to detect a minimal effect size (ρ) of 0.3. The null hypothesis was that $\rho = 0$. We aimed to collect data on approximately 113 patients, to account for incomplete data on up to 10% of them.

Statistical analyses were performed in SAS 9.3 (SAS Institute, Inc., Cary, NC), R (version 0.97.312), and GraphPad Prism (version 5.0a).

RESULTS

Cohort

123 patients were screened for the study's eligibility criteria. 18 patients were excluded, yielding a cohort of 105 patients. Nine patients were excluded for medications, toxins, and comorbidities that could affect the platelet count: 1 had chronic myelogenous leukemia

(CML), 1 had sickle cell disease, 4 had excessive alcohol use within six months of the date of laboratory results, 1 had a recent orthopedic surgery and was on warfarin, 1 had hepatocellular carcinoma, and 1 had a prior splenectomy. Eight patients did not have stored serum available.

The demographic, laboratory, radiologic, and pathologic characteristics of the cohort are shown in Table 1. Platelet count was normally distributed in the cohort.

ELISA Testing

Although we did not test serial samples from each patient, plotting the group's results by year indicated that there was not major degradation of TPO, vWF, or GC level with storage.

Univariate Analysis

Univariate regression analysis indicated that the platelet count was significantly associated with the following variables: age, ALT, direct bilirubin, total bilirubin, IPF, INR, spleen size, vWF, glycocalicin, fibrosis, and TE. Liver biopsies were available for only 37 patients, but univariate analysis of platelet count versus Ishak fibrosis stage as a categorical variable with seven levels yielded a statistically significant association (P=0.01). Subsequent pairwise comparison (with multiplicity adjustment using Tukey's HSD method) of least squares means by Ishak fibrosis stage showed platelet counts were significantly different between stage 2 versus 6 (P=0.015), and stage 0 versus 6 (P=0.021).

Figures 2A–D display plots of the platelet count vs. the four main predictors of interest (TPO, IgG, IPF, and spleen size). Checking of univariate linearity effects between the main predictors of interest and the platelet count revealed the following. The Pearson correlation coefficient (r) for TPO versus platelet count was −0.011, P=0.91, indicating that there was not a significant univariate relationship. The correlation coefficient for IgG versus platelet count was −0.086, P=0.38. The correlation coefficient for IPF versus platelet count was −0.55, P<0.0001. The correlation coefficient for spleen size versus platelet count was −0.46, P<0.0001. The correlation coefficient for observed TE versus platelet count was −0.51, P<0.0001.

Multivariable Regression

A multiple linear model was used to impute the TE scores where data were missing. The model included two independent predictors, AFP (p<0.0001) and AST (p=0.005) with R^2 of 0.60. The imputed TE scores were used in further model analysis where TE was involved. A sensitivity analysis excluding patients without raw TE scores was performed and the conclusions were consistent with the ones obtained from TE with imputation.

A model fitting platelet count to the four factors of interest (IgG, TPO, IPF, and spleen size) had an intercept of 382.5 and an R^2 of 0.46. Three factors were statistically significant: TPO, spleen size, and IPF.

The multiple regression analysis of platelet count versus the four main predictors of interest and six additional candidate predictors (imputed TE, ALT, INR, Bilirubin, GC, and vWF) yielded an intercept of 367.5 and an R^2 of 0.51. In stepwise selection, the following

predictors were ultimately included: imputed TE score, TPO, IPF, and spleen size. The coefficients and P-values are displayed in Table 2.

To address the possibility of collinearity of TPO and IPF, a variance inflation factor was calculated to be 1.04 (not significant).

Stated another way, the multivariable model indicated that an increase in the TE score of 7.9 kPa was associated with a decrease in the platelet count by 10 K/uL, when controlling for other variables in the model. Similarly, an increase in TPO by 37 pg/mL corresponded with a decrease in the platelet count by 10 K/uL, after controlling for all other variables. An increase in IPF by 0.9% was associated with a decrease in the platelet count by 10 K/uL, holding all other variable constant. An increase in the spleen size by 1.2 cm was associated with a decrease in the platelet count by 10 K/uL, after accounting for all other variables in the model.

P-selectin Staining of Liver Biopsies

Ten liver biopsies were selected for staining of platelets via immunohistochemistry for P-selectin (CD62P). Five patients had Ishak fibrosis scores of 0–1 and five had Ishak fibrosis scores of 5–6. The five biopsies from patients with minimal fibrosis were negative for P-selectin, as were four of the five biopsies from patients with cirrhosis. Only one biopsy from a patient with cirrhosis stained positive, with 26 platelets in 40 high power fields (2.8 platelets per square millimeter). Overall, there was not a remarkable difference between the cirrhotic and noncirrhotic biopsies.

DISCUSSION

This cross-sectional study found that fibrosis, thrombopoietin level, immature platelet fraction, and spleen size are independent predictors of the platelet count in patients with CHC.

These findings confirm prior studies showing that the platelet count decreases with more advanced stages of disease. The fact that fibrosis (as assessed by imputed TE) and spleen size were both independently associated with the platelet count suggests that fibrosis does not merely affect platelets via the development of portal hypertension and hypersplenism. If that were the case, one of the predictors would have fallen out on multivariable analysis. Rather, there may be other mechanisms by which fibrosis affects the platelet count, independent of splenomegaly.

We explored the hypothesis that thrombocytopenia in cirrhotic patients is partially due to sequestration of platelets in the liver by staining a subset of liver biopsies for the platelet marker, P-selectin (CD 62P). However, we did not find a significant difference in numbers of platelets seen on biopsies with and without cirrhosis.

While there was no significant association between the platelet count and thrombopoietin on univariate analysis, the multivariable regression found the platelet count to be independently associated with TPO and IPF. At first glance, the finding of TPO and IPF being independent predictors might lead one to think that fibrosis causes the liver to produce less TPO and the

bone marrow to release fewer reticulated platelets into the periphery. However, TPO was negatively associated with the platelet count, suggesting that thrombocytopenia in CHC patients is not necessarily due to decreased hepatic synthesis of TPO. Rather, TPO levels may be compensatorily increased as the platelet count decreases. Our findings challenge the proposed mechanism of decreased TPO levels or decreased stimulation of the megakaryocytic cell line in the bone marrow as a cause of thrombocytopenia in CHC.[19] IPF was also significantly correlated with platelet count in a negative fashion. This suggests that as the platelet count decreases, IPF increases in a compensatory manner. Of note, the IPF does not need to be corrected for the level of thrombocytopenia, as far as we could see in the literature. The finding of IPF as a significant predictor demonstrates the research potential of this relatively new clinical laboratory test.

Our findings that TPO and IPF are negatively associated with the platelet count on multivariable analysis are in direct contrast with the results from several prior studies[19] However, these negative relationships that we found are consistent with recent findings on the hepatic Ashwell-Morell receptor and the IPF as a marker for cirrhosis. The Ashwell-Morell receptor in the liver binds and removes platelets and induces TPO production through JAK-STAT signaling.[26] Consistent with our findings, the IPF has been shown to be higher in patients with cirrhosis compared to healthy controls.[25] While some previous reports have focused on patients with cirrhosis only, we included patients across the spectrum of disease stage. It is possible that in earlier stages of fibrosis, the TPO level and IPF increase in response to a decreasing platelet count but once the liver is cirrhotic, TPO levels decline and the bone marrow produces fewer reticulated platelets. Another difference between our study and others is the inclusion of a multiple regression analysis.

As in other studies, the spleen size was indirectly correlated with the platelet count in a linear fashion. Surprisingly though, IgG was not significant on multivariable analysis, bringing into question the classical teaching that platelets are opsonized by immunoglobulin and sequestered in the spleen. This raises the possibility of another mechanism of splenic consumption of platelets, such as opsonization by specific antiplatelet antibodies. In planning this study, however, our review of the literature did not find antiplatelet antibodies to be related to thrombocytopenia in CHC. Furthermore, total IgG is a test widely used by hepatologists and thus understanding its relationship with the platelet count is of clinical value.

Furthermore, vWF was not significant in the multivariable model, questioning the contribution of endothelial dysfunction in causing thrombocytopenia. This is perhaps because we excluded patients with hepatocellular carcinoma, a group included in other studies.[10]

There were several limitations to this study. Liver biopsies were not available for most patients, and TE was available for a limited number of patients. Therefore, imputation was used to handle missing data. The clinicians performing TE were not blinded to biopsy results, creating a potential for bias in TE measurement. Our study was cross-sectional in nature, and therefore assessment of causality is not possible. Furthermore, our sample size was not sufficiently large to allow for validation of the developed multivariable models.

Because of our study design, we selected independent variables that had potentially important physiologic relationships with the platelet count. We did not include variables such as HCV genotype or viral load.

One objective of the study was to determine if there are unknown factors influencing the platelet count in CHC. The R^2 of our multivariable regression model was 0.51, suggesting that indeed there are other contributing factors which were not included in the model. We did not include antiplatelet antibodies in our study because of prior evidence that they are not responsible for thrombocytopenia in CHC, but there is conflicting evidence on this point.[11, 18] One possible mechanism affecting the platelet count in CHC is that HCV infects the bone marrow. Another potential mechanism is that platelets are increasingly sequestered in a fibrotic liver, though this was not apparent in our examination of liver biopsies stained for platelets. This study demonstrates that while several mechanisms are known, they do not provide a full explanation for the observed phenomenon of thrombocytopenia in CHC patients.

CONCLUSIONS

In conclusion, the results from this study have allowed us to refine our conceptual model of the platelet count in patients with CHC (Figure 3). A deeper understanding of platelet physiology in CHC may inform our thoughts about platelets in other liver diseases such as nodular regenerative hyperplasia, where platelets are often low despite intact synthetic function and in the absence of fibrosis. Future studies focusing on the specific effects of fibrosis and splenomegaly on platelets may shed light on the pathophysiology of thrombocytopenia in patients with CHC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CHC	chronic hepatitis C
HCV	hepatitis C virus
IgG	immunoglobulin G
IPF	immature platelet fraction
TE	transient elastography

TPO	thrombopoietin
vWF	von Willebrand Factor

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HIGHLIGHTS

- Patients with chronic hepatitis C often have thrombocytopenia, but its etiology is incompletely understood.
- This study tested stored serum samples for thrombopoietin, glycocalicin, and von Willebrand Factor.
- Multivariable regression modeling was used to gain insight into the factors associated with the platelet count.
- This cross-sectional analysis determined that fibrosis, thrombopoietin level, immature platelet fraction, and spleen size are independently associated with the platelet count in patients with chronic hepatitis C.

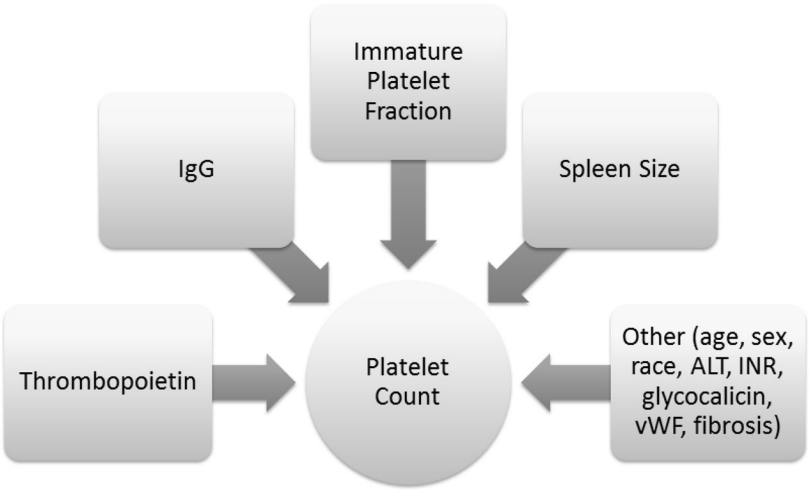
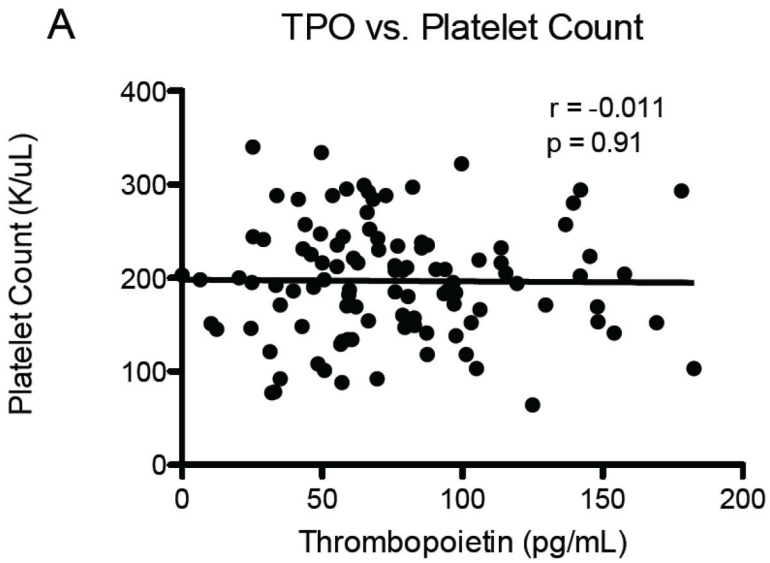
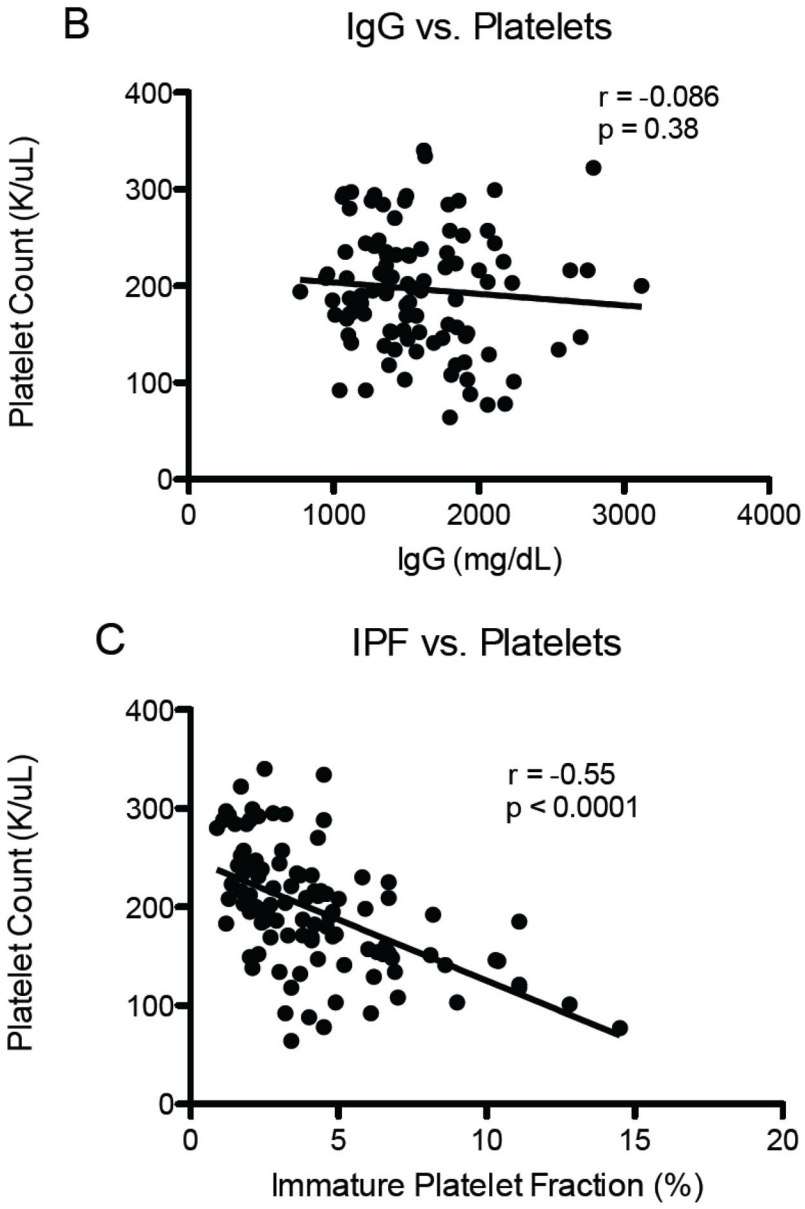


Figure 1.
Conceptual Model of Factors Affecting the Platelet Count in Chronic Hepatitis C.





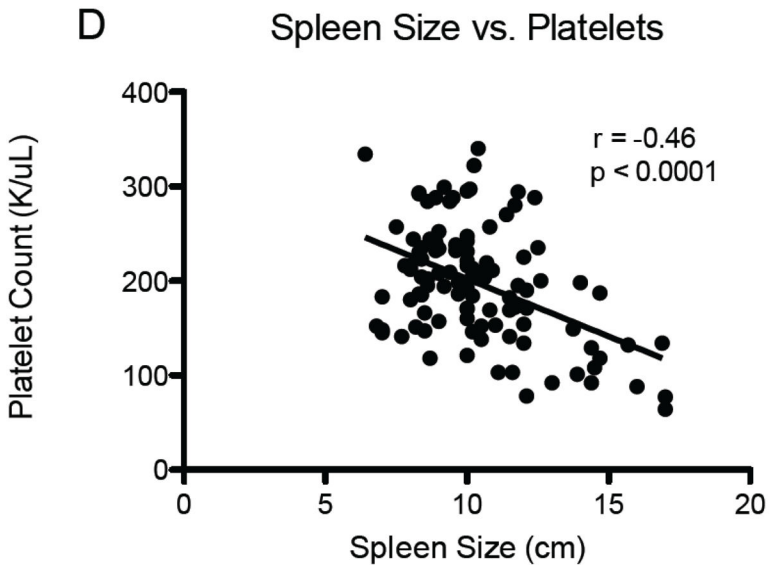


Figure 2.

Figures 2A–D. Univariate Correlation Plots of TPO, IgG, IPF, and Spleen Size versus Platelet Count.

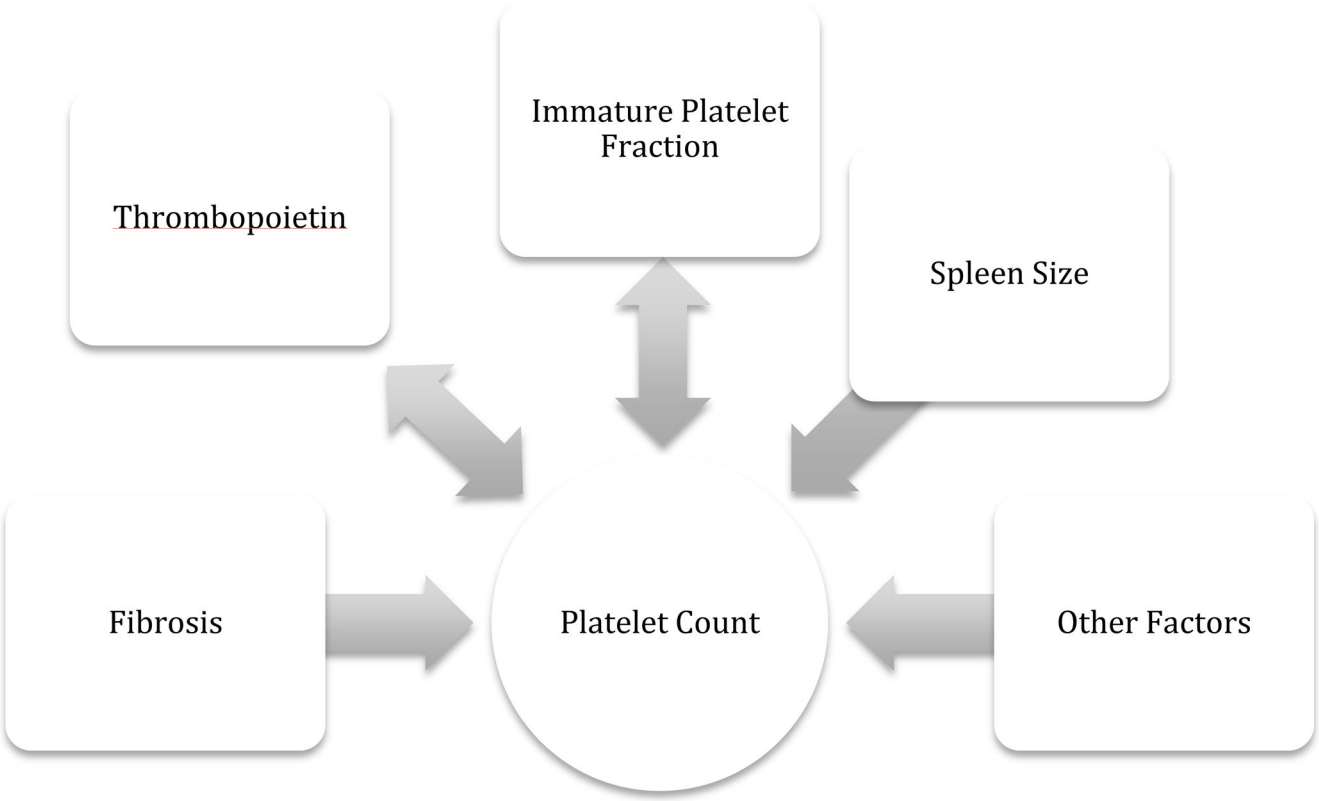


Figure 3.
Revised Theoretical Model of Factors Affecting the Platelet Count in Chronic Hepatitis C.

Table 1

Characteristics of the Cohort. N=105 except where noted. Mean ± SD or absolute number (%).

Age (years)	**51.8 ± 10.8**
Gender	
Female	49 (47%)
Male	56 (53%)
Race	
White	40 (38%)
Black	34 (32%)
Asian	22 (21%)
Other	9 (9%)
ALT (U/L)	93 ± 69
Immature Platelet Fraction (%)	4.2 ± 2.7
IgG (mg/dL)	1578 ± 446
Spleen Size (cm)	10.4 ± 2.3
Ishak Fibrosis Stage, N=37	2 ± 2
TE Score (kPa), N=68	9.3 ± 6.6
Platelet Count (K/uL)	197 ± 61

Table 2

Significant Variables from Multivariable Model including Ten Candidate Predictors, Platelet Count as Outcome. R^2=0.51.

Variable	Coefficient	P-value
Imputed TE	−1.26	0.0032
TPO	−0.27	0.0189
IPF	−10.98	<0.0001
Spleen Size	−8.68	<0.0001