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Thrombocytopenia in Non-Alcoholic Fatty Liver Disease (NAFLD)

Sarah Tomassetti[1,2*], David Yashar[1], Katie LaBarbera[2], Elaina Van Patten[3]

[1]Department of Hematology and Oncology, Harbor-UCLA Medical Center and the David Geffen School of Medicine at UCLA, USA
[2]Department of Hematology and Oncology, The Lundquist Research Institute, USA
[3]Department of Radiology, Harbor-UCLA Medical Center and The David Geffen School of Medicine at UCLA, USA

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is quickly becoming the most common liver disease worldwide, with Hispanic persons being the most effected. Current studies have shown conflicting results as to the incidence of thrombocytopenia in patients with NAFLD. In this study, we aimed to evaluate the incidence of thrombocytopenia in patients with NAFLD in a large Los Angeles safety-net hospital. To do this, we performed a retrospective chart review of adult patients with the diagnosis of NAFLD based on imaging. Patients were excluded if they had cirrhosis, chronic viral hepatitis, splenomegaly, excessive alcohol consumption, malignancy, consumption of drugs commonly associated with thrombocytopenia, or known immune thrombocytopenia. We identified 560 patients with NAFLD. Of those patients, 51.3% were Hispanic. The mean platelet count was 252.4 K/cumm for all patients and 247.1 K/cumm for Hispanic patients. There was no significant difference between Hispanic and non-Hispanic patients. Forty-five (8.04%) patients had thrombocytopenia. Rates of thrombocytopenia were significantly different between the Hispanic (62.2%) and non-Hispanic (11.1%) patient groups (p=0.032). The mean BMI was 33.1 for the study population overall and there was no significant difference among Hispanic and non-Hispanic patients. Coexisting hypertension, CKD, CVD, and OSA occurred in 39.6%, 11.3%, 8.0%, and 4.6% respectively. These rates were not statistically different between Hispanics and non-Hispanics. Further studies are warranted to elucidate the mechanism of decreased peripheral platelet counts in patients with NAFLD.

Keywords: Non-alcoholic fatty liver disease, thrombocytopenia, thrombopoietin

INTRODUCTION

Platelets are a nucleate cells made in the bone marrow that are responsible for the initiation of the hemostatic system and ultimately the repair of damaged endothelium. It is well established that chronic liver disease (CLD) from alcohol use and viral hepatitis negatively affect the peripheral platelet count [1,2]. Possible causes include portal hypertension with splenic sequestration, increased destruction of platelets in the spleen due to autoantibodies (e.g., HCV), direct toxicity on the bone marrow from the underlying etiology (e.g., HCV or alcohol), and decreased thrombopoietin (TPO) [3-7]. Less is known about the effects of non-alcoholic fatty liver disease (NAFLD) on the peripheral platelet count.

NAFLD is a nonalcoholic fatty liver disease characterized by excessive fat accumulation in the liver with or without inflammation and fibrosis. By definition, no secondary cause of hepatic steatosis is present. NAFLD is subdivided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, hepatic steatosis is present without evidence of significant inflammation. In NASH, hepatic steatosis is associated with hepatic inflammation that may be histologically indistinguishable from alcoholic steatohepatitis [8].

NAFLD is quickly becoming the most common liver disease worldwide. In the United states, the estimated prevalence of NAFLD is 25% with Hispanics having the highest prevalence [9,10]. It is associated with lack of physical activity and unhealthy eating habits. Patients often have components of

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Corresponding author Sarah Tomassetti, Department of Hematology and Oncology, Harbor-UCLA Medical Center and the David Geffen School of Medicine at UCLA, USA, E-mail: sarah.tomassetti@gmail.com

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metabolic syndrome including obesity, systemic hypertension, dyslipidemia, and insulin resistance or overt diabetes [9,11]. In the US, the prevalence of the components of metabolic syndrome and NAFLD has also been increasing over time [9,11]. Approximately, 20%-30% of patients with NAFLD will develop NASH. A subset of individuals with NAFLD develops progressive liver disease characterized by hepatocyte injury, inflammation, and ultimately cirrhosis. It is an important cause of cryptogenic cirrhosis.

NAFLD is mainly a diagnosis of exclusion. The diagnosis requires evidence of hepatic steatosis by imaging or biopsy, absence of excessive alcohol intake or coexisting chronic liver disease, and exclusion of other causes of hepatic steatosis. Imaging such as ultrasonography often reveals a hyperechoic texture or a bright liver due to diffuse fatty infiltration. The definite diagnosis of NAFLD is ideally done *via* biopsy, which is an invasive procedure with complications. There are several noninvasive alternatives to diagnosing, each with different sensitivities and accuracies [12-15].

The current literature shows conflicting results as to the association of NAFLD and thrombocytopenia [16-22]. Furthermore, only two small studies included primarily Hispanic patients, who are known to be at increased risk of NAFLD compared to other ethnicities [21,22]. A larger study looking at the association between platelet count and NAFLD is warranted.

In this study, we aimed to evaluate whether patients with NAFLD have thrombocytopenia. In particular, we aimed to look at whether there would be an association between NAFLD and platelet count in a county, mostly ethnic minority, population.

METHODS

We performed a retrospective chart review of all patients aged greater than 18 years who presented to Harbor-UCLA Medical Center between October 1, 2015 and March 1, 2021 with the diagnosis of NAFLD.

Patients were excluded if they had cirrhosis, chronic viral hepatitis, splenomegaly, excessive alcohol consumption (≥ 30 g/day in men or ≥ 20 g/day in women), malignancy, consumption of drugs commonly associated with thrombocytopenia, or known immune thrombocytopenia.

The diagnosis of NAFLD was established based on radiologic evidence of NAFLD on abdominal ultrasound or computed tomography scan. Hepatic ultrasound was read by experienced radiologists, who commented on the overall appearance of the liver. No specific grading protocol was performed. Several factors were analyzed; the length of the liver (> 17 cm is enlarged), echotexture (difference in echogenicity of the liver from the renal cortex/spleen, commenting on severity from mild to severe as well as diffuse vs focal), surface nodularity, hepatic vein appearance, presence of focal lesions, evidence of portal hypertension, and evaluation of the gallbladder for other sources of hepatic injury. The diagnosis of hepatic steatosis is supported by hepatomegaly, increased liver echogenicity, and possible obscuration of the hepatic vessels.

Some patients had hepatic steatosis diagnosed based on CT imaging. Experienced radiologists compared the attenuation of the liver to the spleen on non-contrast imaging. The diagnosis of steatosis is supported when the liver is less than 10 Hounsfield units (HU) than the spleen. On contrast imaging, absolute Hounsfield units of <40 was used. As with ultrasound, the radiologists noted any evidence of cirrhosis or portal hypertension, including liver surface nodularity, hepatomegaly, ascites, or splenomegaly. These patients with evidence of cirrhosis or portal hypertension were excluded from the study. They also noted the pattern of fat deposition and examined for any focal lesions.

Platelet count, body mass index (BMI), bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, protein, cholesterol, triglycerides, prothrombin time (PT), partial thromboplastin time (PTT), and HbA1c were measured. Comorbid conditions including hypertension, obstructive sleep apnea (OSA), cardiovascular disease (CVD), and chronic kidney disease (CKD), were also recorded. Thrombocytopenia was defined as a platelet count of <150 K/cum. Overweight was defined as a BMI between 25 kg/m^2 and 29.9 kg/m^2 with obesity defined as a BMI or 30 kg/m^2 and above.

Descriptive analysis was used to describe and characterize the patient population as well as the Hispanic subgroup. Pearson chi-square tests using SPSS were performed to look for associations between thrombocytopenia and comorbidities on the entire study population as well as for the Hispanic patient group only. Continuous numeric variables such as BMI, HbA1c, and total cholesterol were dichotomized into clinically relevant categories in order to perform the test for association of these comorbidities with thrombocytopenia. These dichotomies are as follows: Obese vs. not obese, diabetic vs. not diabetic, and hyperlipidemic vs. not hyperlipidemic, based on standard clinical laboratory values. An independent samples t-test was used to determine whether these characteristics were statistically different between the Hispanic and non-Hispanic patient population. Patients with an unknown ethnicity were excluded from the analysis of differences between Hispanic and non-Hispanic patients. Association was determined by comparing the 2-sided p-value with the nominal significance level of 0.05. The asymptotic p-value was reported as long as the expected counts for the chi-square cross tabulation were above 5 subjects, if fewer than 5 subjects were expected then the Fischer's Exact Test was used to obtain the p-value.

RESULTS

There were a total of 560 patients with the diagnosis of NAFLD who met the inclusion criteria. The percentage of female and male patients was 58.9% and 41.1%, respectively. Of these, 51.3% were Hispanic, 8.9% were White European, 6.9% were African American, 2.9% were Asian, 2.5% were Southeast Asian, 1.6% was Native American/Pacific Islander, 1.1% were Middle Eastern and 24.8% were unknown. The average age was 50 years.

The mean platelet count was 252.4 K/cumm. The range was 81 K/cumm-716 K/cumm. Among Hispanic patients the mean platelet count was 247.1 K/cumm and the range was 85 K/cumm-716 K/cumm. 45 (8.04%) patients had thrombocytopenia, 28 (62.2%) of whom were Hispanic. The mean platelet count was not significantly different between Hispanics and non-Hispanics. However, the rates of thrombocytopenia

were significantly different between the Hispanic (62.2%) and non-Hispanic (11.1%) patient groups (p=0.032), with 26.7% of patients of unknown ethnicity having thrombocytopenia.

The mean BMI was 33.1 for the study population overall. The mean AST was 44.9 (normal 15 U/L-41 U/L) and ALT was 57.5 U/L (normal 7 U/L-35 U/L). The mean bilirubin, albumin, protein, PT, and PTT were all within normal limits. There was not significant difference for these means among Hispanic and non-Hispanic patients.

The mean HbA1c was 6.89% overall. The mean total cholesterol was 179.2 mg/dL (normal 125 mg/dL-199 mg/dL), HDL 44.2 mg/dL (normal >40 mg/dL), and LDL 101.9 mg/dL (normal <99 mg/dL).

Coexisting hypertension, CKD, CVD, and OSA occurred in 39.6%, 11.3%, 8.0%, and 4.6% respectively. These rates were not statistically different between Hispanics and non-Hispanics.

Thrombocytopenia was not statistically associated with obesity (p=0.160), diabetes (p=0.779), or hyperlipidemia (p=0.237). Thrombocytopenia was associated with hypertension (p=0.01). The odds ratio for having hypertension as a comorbidity with thrombocytopenia was 1.52 with a 95% confidence interval of (1.16,2.0). Among Hispanic patients, thrombocytopenia was not statistically associated with any of the comorbidities of interest, all p-values obtained were greater than 0.05.

DISCUSSION

There are conflicting results in the literature as to the association between NAFLD and thrombocytopenia. In this study, we found that 8.04% of patients with NAFLD have thrombocytopenia.

There have been a few other studies showing low rates of thrombocytopenia in NAFLD patients. A large retrospective study conducted in Brazil of 440 patients with biopsy-proven NASH without cirrhosis showed a prevalence of thrombocytopenia of 3.2% [20]. The average platelet count was not reported. Similarly, a study conducted in Iran that included 1305 patients with NAFLD found the prevalence of thrombocytopenia of 2.4% [18]. The average platelet count of all patients with NAFLD was 256 × 109/L [18].

Hispanic patients have the highest rate of NAFLD. Our study consisted of over half Hispanic patients. Interestingly, we found that Hispanic patients had a statistically significant higher incidence of thrombocytopenia than non-Hispanic patients (62.2 versus 11.1%, respectively). To our knowledge, there have been only 2 other studies looking at the incidence of thrombocytopenia in primarily Hispanic patients with NAFLD.

A study conducted in Mexico identified 78 patients with NAFLD, of which 22 (28%) had thrombocytopenia (defined here as a platelet count less than 100/L × 109/L) [22]. In patients with both insulin resistance and NAFLD, the incidence of thrombocytopenia increased to 65% [22]. These investigators used more strict criteria to define NAFLD that was based on serologic determinations combined with liver transient elastography. This could account for the higher rate of thrombocytopenia in these patients. Another study conducted in Mexico that included 33 patients with NAFLD using similar diagnostic criteria found thrombocytopenia in 8 (24%) patients (thrombocytopenia here was defined as a platelet count less than 150/L × 109/L) [21]. The average platelet count of the 8 patients with thrombocytopenia was 101.5/L × 109/L (range 53/L-126/L × 109/L [21]. These studies are the only ones to our knowledge consisting of primarily Hispanic patients. Interestingly, these studies show substantially higher rates of thrombocytopenia than studies conducted in Brazil and Iran [18,20] suggesting possible higher rates of thrombocytopenia in Hispanic patients with NAFLD.

In our study, the mean platelet count was not significantly different between Hispanics and non-Hispanics. In contrast, there have been several studies that did show significantly decreased platelet counts in patients with NAFLD. A large study conducted in China compared platelet counts in 1303 patients with NAFLD and without NAFLD and found that mean baseline (**Tables 1 and 2**). Platelet counts were significantly lower in patients with NAFLD (220 versus 213/L × 109/L (P=0.0023) [16]. However, the mean platelet count remained within normal limits. Patients with NAFLD had significantly higher BMI and rates of hypertension, hypertriglyceridemia, and diabetes [16]. A study conducted in the United States similarly showed significantly lower platelets (218.4 versus 255.3) in patients with NAFLD compared to controls, but the average platelet counts remained within normal limits [17]. The incidence of thrombocytopenia was not reported in these studies.

Table 1: Baseline characteristics

Characteristic	N=560
Age (yr)	50
Female sex (%) Ethnicity	58.9
Hispanic (%)	51.3
White (%)	8.9
African American (%)	6.9
Asian (%)	2.9
Southeast Asian (%)	2.5
Native American/Pacific/Islander (%)	1.6
Middle Eastern (%)	1.1
Unknown (%) Ethnicity	24.8

Table 2: Baseline

Characteristic	
Platelet count all	252.4 K/cumm
Platelet count Hispanic	247.1 K/cumm
Thrombocytopenia all	8.04%
Thrombocytopenia	
Hispanic	62.20%
Non-hipanic	11.10%
Unknown	26.70%
BMI	33.1
HbA1c	6.89%

The differences between the results of these studies can possibly be explained by the use of various diagnostic methods, population sizes, and inclusion criteria. Although liver biopsy remains the gold standard for the diagnosis of NAFLD, it is an invasive and rarely performed procedure for the diagnosis of NAFLD. While some studies based the diagnosis of NAFLD on ultrasound imaging, similar to our study, other studies used only

patients with biopsy-proven NAFLD or more sensitive imaging techniques such as transient elastography in combination with or without serologic criteria. The population sizes also differed widely. Lastly, some studies included some patients with some evidence of fibrosis.

Thrombocytopenia (**Table 3**) in NAFLD may be attributed, in part, by inadequate TPO production in the failing liver. TPO is a glycoprotein made by the liver, and to a lesser extent the kidneys, spleen, and bone marrow, that regulates platelet production. By binding to its receptor, c-MPL, expressed on the surface of stem cells, megakaryocyte progenitor cells, megakaryocytes, and platelets, TPO acts on all stages thrombopoiesis to regulate the development and function of megakaryocytes and their release of platelets [23,25]. TPO production is based on functional liver cell mass and is mostly constitutive; TPO mRNA levels are not increased in the setting of thrombocytopenia [26]. Instead, the TPO level is determined by circulating platelet mass. When TPO binds to c-MPL receptors on megakaryocytes and platelets, it is removed from circulation. In the setting of thrombocytopenia (e.g., following chemotherapy), there is an insufficient number of platelets to remove TPO from circulation. This results in decreased TPO clearance and an increased amount of circulating TPO that stimulates megakaryocyte growth. In contrast, in the setting of other liver diseases, such as NAFLD, TPO production may also be reduced which could result in lower platelet counts. Further studies assessing TPO levels in these patients may be useful.

Table 3: Chi Square analysis of comorbidity in identifying thrombocytopenia

Comorbidity	Patients without thrombocytopenia	Patients with thrombocytopenia	P Value
Hypertension	39.60%	57.70%	0.01
Chronic kidney disease	10.70%	17.70%	0.277
Cardiovascular disease	7.40%	15.50%	0.152
Obstructive sleep apnea	4.90%	2.20%	0.736
Hyperlipidemia	7.80%	2.20%	0.237
Diabetes	62.30%	64.40%	0.779
Obesity	63.90%	53.30%	0.16

CONCLUSION

In conclusion, this paper is one of the first large studies looking at NAFLD and thrombocytopenia in a county population consisting of primarily Hispanic patients. We found that approximately 8.04% of patients with NAFLD had concurrent thrombocytopenia. Importantly, the Hispanic patients with NAFLD had significantly higher rates of thrombocytopenia than non-Hispanic patients. There was no association found between thrombocytopenia and obesity, diabetes, or hyperlipidemia. However, patients with thrombocytopenia were more likely to have hypertension. Further studies looking at TPO levels in NAFLD patients may be useful.

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AUTHORS CONTRIBUTION

S.T and D.Y. designed the study; D.Y. collected the data; K.L. performed the data analysis; E.V.P. assisted in writing the manuscript; S.T. wrote and edited the manuscript; and all coauthors reviewed the paper and added substantial contributions.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

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