MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 9882-9886
DOI: 10.12659/MSM.920172

Received: 2019.09.19
Accepted: 2019.10.10
Published: 2019.12.23

Evaluation of Plateletcrit and Platelet Distribution Width in Patients with Non-Alcoholic Fatty Liver Disease: A Retrospective Chart Review Study

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Source of support: Departmental sources

Background: Platelets are considered to be essential in proinflammatory environments, including atherosclerosis. The degree of platelet activation has been demonstrated to be correlated with plateletcrit and platelet distribution width. The main purpose of this study was to assess the relationship between plateletcrit (PCT), platelet distribution, and the degree of hepatic steatosis in patients with non-alcoholic fatty liver disease (NAFLD).

Material/Methods: We enrolled 225 biopsy-proven NAFLD patients and 142 control subjects without NAFLD. NAFLD patients were separated into 2 groups according to percentage of steatosis. Demographic and clinical data were collected retrospectively.

Results: PCT level was significantly higher in NAFLD group I and group II than in the control group. PCT was higher in the NAFLD groups than in the control group. However, there was no difference according to PCT and PDW levels between NAFLD groups.

Conclusions: In this study, a relationship was found between PCT and hepatosteatosis, but no relationship was found with PDW. PCT might be a useful biomarker for early detection of steatohepatitis in patients with nan-alcoholic fatty liver disease.

MeSH Keywords: Liver Diseases • Platelet Activation • Platelet Count

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/920172

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Background

Non-alcoholic fatty liver disease (NAFLD) is a common disease that can range from simple steatosis to non-alcoholic steatohepatitis (NASH) [1]. Patients with NAFLD have a high risk for progression to severe and decompensated liver disease comprising cirrhosis and hepatocellular carcinoma. During the course of disease, detecting early stages of NASH is very important. The main method for assessment of inflammation and fibrosis is liver biopsy. Nevertheless, other non-invasive methods are needed.

Recent studies have highlighted the critical role of platelets in inflammation [2–5]. Activated platelets and platelet-derived microparticles by various factors can play an important role in inflammation by stimulating proinflammatory substances such as chemokines, cytokines, and nitric oxide [2]. Platelet distribution width (PDW) characterizes the range of difference in platelet size and large PDW can be a sign of inflammation. Plateletcrit (PCT) is analogous to the hematocrit and reflects the proportion of volume platelets in whole blood. Recent studies showed the association between PCT and PDW with inflammation [6,7]. Therefore, PCT and PDW could be predictors of the degree of hepatic steatosis and inflammation in patients with NAFLD.

The aim of this study was to investigate the relationship between PCT and PDW levels between the degree of liver steatosis and inflammation in patients with NAFLD.

Material and Methods

We retrospectively evaluated data of living donor applicants who received liver biopsies between 2010 and 2019 at the Demiroglu Bilim University Istanbul Gastroenterology Department. The study was approved by the Demiroglu Science University Ethics Committee. Informed consent was obtained from all study patients and control group members.

All of the living donor candidates underwent ultrasonography, computed tomography, and magnetic resonance imaging evaluation. When pretransplant imaging showed evidence of moderate or severe fatty liver, preoperative liver biopsy was performed. Any level of the steatosis is essential for either NAFLD or NASH according to definition. According to the histopathological findings, the patients were divided into 2 groups; 225 patients biopsy-proven NAFLD and 142 control subjects without NAFLD. The NASH Clinical Research Network was the main classification for specimens [8]. Patients with NAFLD were separated into 2 groups according to the steatosis levels: Group I had 1–20% and Group II had >20%.

The inclusion criteria were age (18–65 years), no immoderate alcohol history (consumption of ethyl alcohol is >30 g/day for males, >20 g/day for females per a day), and negativity for viral hepatitis markers. The exclusion criteria were cirrhosis, diabetes mellitus, cardiovascular diseases, asthma, hematologic problems, infections, previous cancer history of liver transplantation, drug-induced hepatosteatosis, or refusal to participate in the research. Demographic and anthropometric data were recorded, including age, sex, and body mass index (BMI), as well as serum biochemistry tests such as total bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total cholesterol (TC), triglycerides (TG), platelet count (PLT), PCT, mean platelet volume (MPV), and PDW. The Homeostatic Model of Assessment HOMA-IR, a measure of insulin resistance, sets a level of ≥2.5 to define insulin resistance [9].

Data are expressed as mean±standard deviation (SD). SPSS 21.0 (SPSS, Inc., Chicago, USA) was used for biostatistical analysis (means, standard deviations, ranges, and percentages). The Kolmogorov-Smirnov test was used for distribution. The Mann-Whitney U test was used for continuous variables, and ANOVA and Kruskal-Wallis tests were used to compare more than 2 groups. Pearson's (continues variables) and Spearman's (categorical variables) analyses were used for bivariant correlations. The level of significance was set a two-tailed P value >0.05.

Results

A total of 367 patients were enrolled. The mean (±SD) age of the patients was 34.08±9.08 years in the NAFLD group and 34.24±8.72 years in the control group. There were 187 males (61.4%) and 180 females (58.6%) in the NAFLD group and 81 males (57.1%) and 59 females (42.9%) in the control group. There were no significant differences between the 2 groups in age or sex distribution. The total bilirubin, GGT, albumin, MPV, and PDW levels were similar in the 2 groups. However, BMI, ALT, ALP, AST TC TG, HOMA-IR, PLT, and PCT values were higher in patients with NAFLD than in the control group. Comparison of laboratory, clinical, and demographic data of patients and control groups are summarized in Table 1.

Correlations between the stage of steatosis and laboratory parameters, including PCT, PLT, and MPV, were also tested. PCT level was positively correlated with the severity of steatosis in patients with NAFLD, and PLT and MPV levels showed positive but weak correlations with steatosis in NAFLD patients. However, PDW level did not show any correlation with the stage of steatosis (Table 2).

Table 3 compares the variables among 3 groups (control and NAFLD groups I-II). Kruskal-Wallis testing showed that PCT levels were significantly different among the 3 groups (p<0.001).

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Table 1. Laboratory, clinical, and demographic data of NAFLD patients and controls.

	NAFLD (n=225)	Control (n=142)	P*
Age	34.08±9.08	34.24±8.72	0.80
Sex (Female/Male. n)	87/138	61/81	0.41**
Body mass index (kg/m^2)	24.71±3.34	27.25±4.02	<0.001
ALT (IU/L)	18.47±10.88	22.76±14.13	0.001
AST (IU/L)	16.99±4.60	18.48±5.66	0.015
ALP (U/L)	66.11±20.06	72.92±24.40	0.009
GGT (U/L)	18.23±12.33	20.72±15.76	0.10
Total biluribin (mg/dl)	0.59±0.53	0.59±0.31	0.17
Albumin (g/dll)	4.66±0.61	4.68±0.31	0.10
Triglyceride (mg/dL)	96.54±43.79	117.74±66.10	0.03
Total cholesterol (mg/dl)	178.90±45.13	185.79±41.36	0.03
HOMA-IR	1.71±0.77	2.60±1.61	<0.001
PLT (10^3/µL)	234.86±62.56	248.56±63.44	0.03
PCT (%)	0.22±0.06	0.25±0.06	<0.001
MPV (fL)	10.05±0.92	10.09±0.95	0.45
PDW (fL)	11.83±1.67	12.01±2.01	0.89

ALT – alanine aminotransferase; AST – asspartate aminotransferase; ALP – alkaline phosphatase; GGT – gamma-glutamyl transferase; PLT – platelet count; PCT – plateletcrit; MPV – mean platelet volume; PDW – platelet distribution width; HOMA-IR – homeostatic model assessment insulin resistance. * Mann-Whitney Test, ** χ^2 test.

Table 2. Correlation analysis between hematologic parameters and NAFLD stage.

	NAFLD degree	
	r	P*
PLT (10^3/µL)	0.110	0.036
PCT (%)	0.243	<0.001
MPV (fL)	0.116	0.026
PDW (fL)	0.069	0.187

PLT – platelet count; PCT – plateletcrit; MPV – mean platelet volume; PDW – platelet distribution width. * Spearman correlation.

PLT, MPV, and PDW values were similar in all 3 groups. PCT value was significantly different between group I and the control group, as well as between group II and the control group. No significant difference was detected regarding PLT, PDW, and MPV values between group I and the control group and between group II and the control group. Furthermore, there was no significant difference detected according to PCT, PLT, PDW, and MPV values between group I and II.

Discussion

To the best of our knowledge this is the first research that evaluate the relationship between PCT and PDW levels and

Table 3. The comparison of hematologic parameters between NAFLD group I–II and control group.

	Group I (n=201)	Group II (n=24)	Control (n=142)
PLT (10^3/µL)	248±62.94	253.29±68.22	234.86±62.56
PCT (%)	0.25±0.0*	0.27±0.01*	0.22±0.60
MPV (fL)	10.04±0.06	10.47±0.16	10.05±0.07
PDW (fL)	11.97±2.03	12.36±1.89	11.83±1.67

* Kruskal-Wallis test; p<0.05 versus control. PLT – platelet count; PCT – plateletcrit; MPV – mean platelet volume; PDW – platelet distribution width.

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hepatic steatosis in biopsy-proven NAFLD patients. We found that NAFLD patients had notably higher PCT levels than the healthy control group. PCT levels were significantly elevated according to the degree (percentage) of hepatic steatosis. In addition, the PLT and MPV levels were also mildly higher than in healthy control. Nevertheless, in contrast to most previous studies, PDW levels were not associated with the degree of hepatic steatosis.

NAFLD is the main cause of chronic liver disease worldwide. A recent large multiethnic cohort study found that NAFLD is the major cause of chronic liver disease and cirrhosis [10]. Due to the limitations of non-invasive testing in NAFLD patients, liver biopsy remains the criterion standard for NAFLD staging. However, it has many drawbacks, including high cost, inadequate sampling, invasiveness, and risk of complications (e.g., bleeding, biliary peritonitis, gall bladder perforation). Therefore, novel basic, cost-effective, and safe diagnostic tools or tests are needed.

Many researchers indicated that platelets play a key role in the pathogenesis of inflammation by collaborating with leukocytes and endothelium, or releasing mediators, which triggers inflammation. Large thrombocytes are more massive than small thrombocytes, and they have a more active metabolism and enzyme activity [5,6]. PCT and PDW are simple platelet indices that increase during platelet activation.

Recent studies showed a relationship between PCT and both acute and chronic diseases, including juvenile rheumatoid arthritis, autoimmune gastritis, acute coronary syndromes, inflammatory bowel diseases, hyperemesis gravidarum, and acute hepatitis A [11–16]. Reviewing the literature, only 2 studies were published that investigated the association between PCT and NAFLD. The first study was a large population-based study from China that evaluated PCT levels in female patients with non-biopsy-proven NAFLD; the authors suggested that serum PCT level is an independently significant predictor of NAFLD development [17]. The second study showed similar results. They showed that the PCT levels were higher in NAFLD rather than control group. However similar to our study, they have found no significant differences between PCT levels and the degree of liver steatosis [18]. These 2 studies had some limitations. The first study, the authors only investigated females and both of the 2 studies were not evaluated in biopsy-proven NAFLD patients. In contrast, the present study only included the biopsy-proven NAFLD and non-NAFLD patients and included males and females.

PDW characterizes the changeability in thrombocyte size and delivers more information than MPV as regards platelet reactivity. To date, only 2 studies have investigated the relationship between NAFLD and PDW levels. The first study, by Milovanovic et al., showed that PDW levels were much higher in NAFLD patients than in the control group [18]. However, Sarami et al. showed that PDW levels were similar between healthy controls and NAFLD patients [19], and in agreement with this, we also found that PDW levels were not different between NAFLD patients and the control group. These 2 previous studies were limited by their small sample sizes and lack of biopsy-proven NAFLD patients. The large sample size and histological examinations are most important factors contributing to the superior power of our study and its more reliable results.

The exact pathogenesis of NAFLD still remains unclear. However, most authors suggested the "2- hit: model of development of steatohepatitis. The first "hit" is high-fat diet, obesity, insulin resistance, and hepatic lipid accumulation. The second "hit" is liver fibrosis due to inflammatory events [20–22]. It was shown that depletion of liver macrophages leads to decreased lipid droplet accumulation in hepatocytes [23]. Recent research examining arginase 2-deficient mice suggested that inflammation can cause *de novo* hepatic lipogenesis [24]. Therefore, hepatic lipogenesis may lead to free fatty acid production with induction of reactive oxidant species (ROS) production [25]. Some studies found that ROS formation is important for platelet activation [26]. In the present we found that elevated platelet and PCT levels in patients with NAFLD might be explained by these complex pathophysiological mechanisms. Therefore, the aim of medical management of NAFLD should involve reducing platelet activation. In one study, researchers retrospectively analyzed the association between aspirin use and liver fibrosis among patients with chronic liver disease, concluding that aspirin use was associated with lower indices of liver fibrosis [27]. Recently, Simon et al. showed that daily aspirin use was associated with less severe histologic features of NAFLD, as well as decreased risk of fibrosis [28]. Based on these studies, we hypothesized that elevation of platelet levels might also lead to progression of liver steatosis and fibrosis in patients with NAFLD.

The present study has some limitations. Our study was a retrospective single-center study and the number of patients with high degree of steatosis was low.

Conclusions

In conclusion, PCT, but not PDW, is a simple, non-invasive, and useful marker that may be a useful tool for predicting and screening steatosis in patients with NAFLD. In the future, investigators may focus on the role of PCT for predicting and screening the clinical outcome and progression of steatosis in patients with NAFLD.

Conflicts of interest

None.

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