

# The effect of standard therapy on mean platelet volume in patients with chronic hepatitis C

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## Abstract

**Introduction:** Chronic hepatitis C (CHC) infection is a systemic disorder that can lead to liver inflammation, fibrosis, cirrhosis, and hepatocellular cancer. The mean platelet volume (MPV) is widely used as an inflammatory marker to evaluate the platelet function and the status of systemic inflammation.

**Aim:** To determine the pre- and post-treatment MPV values in CHC patients who were administered a 48-week antiviral therapy based on systemic inflammation.

**Material and methods:** We enrolled 28 patients, diagnosed with CHC genotype 1b, who received a 48-week antiviral therapy and attended regular follow-up, and 28 healthy individuals. In diagnosing CHC, a positive anti-HCV for a minimum duration of 6 months and a positive serum HCV RNA were accepted as the criteria. The patients were assigned to one of two groups based on their group 1 (pre-treatment values) and group 2 (post-treatment values) after 3 months therapy. We analysed and compared the blood samples of all of the groups.

**Results:** The MPV value was  $8.89 \pm 1.20$  in group 1 and  $8.00 \pm 1.07$  in group 2, and  $8.21 \pm 1.18$  in the control group. The value in group 1 was detected to be statistically significantly different from that in group 2 and the control group ( $p < 0.0001$ ,  $p = 0.045$ , respectively). No statistically significant difference was observed between group 2 and the control group ( $p = 0.455$ ).

**Conclusions:** The results of this study suggest that MPV could represent an inexpensive marker for use in assessing low-grade inflammation in patients with CHC.

## Introduction

Hepatitis C virus (HCV) is one of the most important causes of chronic liver diseases. Hepatitis C virus is known to have two different processes: acute or chronic, and is seen in approximately 3% of the population worldwide [1, 2]. Acute hepatitis cases may frequently lead to chronic hepatitis C (CHC) infection, liver fibrosis, cirrhosis, and hepatocellular cancer (HCC) [3, 4]. Chronic hepatitis C infection leads to systemic inflammation via steatosis, increased oxidative stress, and pro-inflammatory cytokines [1, 5].

A complete blood count is a relatively routine, inexpensive, practical and easy examination that gives additional information. Platelet activation is a link in

the pathophysiology of diseases prone to thrombosis and inflammation [6]. The mean platelet volume (MPV) is the most commonly used among markers assessing the changes in platelet function and activation [7, 8]. The MPV also indicates inflammatory status, which is central to processes that are involved in inflammatory disease pathophysiology and endothelial dysfunction. Recently, MPV has been shown as an inflammatory marker in various inflammatory diseases [9–12]. A previous study reported that MPV levels are higher in CHC patients and that they are also correlated the activity index in these patients [13].

Based on the literature data, although the relation between the CHC patients and MPV levels were investigated in a previous study [13], the relation between

MPV values and the standard therapy of CHC patients was not determined. Our study is the first to assess the MPV values before and after standard treatment in CHC patients.

## Aim

The aim of the study was to determine the pre- and post-treatment MPV values in CHC patients and investigate its correlation with inflammation.

## Material and methods

In our study, we enrolled 28 patients, diagnosed with CHC genotype 1b, who received 48-week pegylated interferon (Peg-IFN)  $\alpha$ 2a and ribavirin (RBV) (800–1000 mg) and attended regular follow-up, and 28 healthy individuals. In diagnosing CHC, a positive anti-HCV for a minimum duration of 6 months and a positive serum HCV RNA were accepted as the criteria. The patients were assigned to one of two groups based on their pre-treatment values and post-treatment values after 3 months therapy. According to the pre-treatment liver histopathological assessment, patients with a liver fibrosis score (LFS) between 0 and 2 were considered to have a low-grade fibrosis while those with an LFS between 3 and 6 had high-grade fibrosis [14].

Patients with diabetes mellitus, asthma, chronic obstructive pulmonary disease, cirrhosis, portal hypertension, renal dysfunction, peripheral and cerebral vascular disease, splenectomy, splenomegaly, malignancy, and a history of alcohol use and/or smoking were excluded from the present study. The study was conducted in accordance with the Declaration of Helsinki, and local Ethics Committee approval was granted.

### Biochemical measurements

Blood samples were drawn without stasis at 7–8 a.m. after 20 min of supine rest, following fasting for  $\geq 12$  h. The blood was collected in tripotassium EDTA (7.2 mg) tubes. Haematological parameters, including haemoglobin (Hb), white blood cells count (WBC), platelet count, and MPV, were analysed using an LH 780 analyser (Beckman Coulter Inc, Miami, Florida). We analysed the blood samples of all of the groups using an automatic blood counter within 1 h after venipuncture because a delay in the measurement could change the MPV values [15].

### Statistical analysis

All statistical analyses were performed using SPSS version 14.0 (SPSS, Chicago, IL). Descriptive statistics were calculated for each of the variables (means and standard deviation (SD)). Paired sample *t* test was used

to evaluate the statistical data. Also, the non-parametric Wilcoxon Signed Ranks test was used to test for the differences between the related (paired) samples, and the Mann-Whitney *U* test was used to investigate the differences between the independent samples. Spearman's correlation analysis was used to evaluate the correlation between data. A *p* value  $< 0.05$  was considered statistically significantly two sided.

## Results

There were 17 (60.7%) male and 11 (39.3%) female patients in the study, with a mean age of  $53.6 \pm 12.9$  (range: 28–79 years) years. In the control group, there were 13 (46.4%) males and 15 (53.6%) females, with a mean age of  $46.4 \pm 17.4$  years (range: 20–77 years). There were no statistically significant differences between the patients and the control subjects with respect to age and gender ( $p = 0.103$  and  $p = 0.288$ , respectively). The rates of response to treatment, the post-histopathological assessment histologic activity index (HAI), and hepatic steatosis as detected by LFS and the abdominal ultrasonography (grade 1) are reported in Table I. The laboratory values in group 1 (pre-treatment) and group 2 (post-treatment) are given in Table II.

The comparison of certain parameters between group 1, group 2, and the control group is summarised in Tables III and IV. The MPV value was  $8.89 \pm 1.20$  in group 1,  $8.00 \pm 1.07$  in group 2, and  $8.21 \pm 1.18$  in the control group. Baseline MPV values were higher in patients with CHC compared with those of controls (Figure 1) ( $p = 0.045$ ). Compared to group 2, group 1 had significantly different MPV levels (Figure 2) ( $p < 0.001$ ). No statistically significant difference was observed between group 2 and the control group ( $p = 0.455$ ). The

**Table I.** The baseline clinical characteristics of the patients

| Treatment response                               | Result          |
|--|-----------------|
| Sustained virological response, <i>n</i> (%)     | 12 (42.9)       |
| Non-sustained virological response, <i>n</i> (%) | 16 (57.1)       |
| Abdominal ultrasonography:                       |                 |
| Normal, <i>n</i> (%)                             | 19 (67.9)       |
| Hepatosteatosis, <i>n</i> (%)                    | 9 (32.1)        |
| Liver fibrosis score 0–2, <i>n</i> (%)           | 11 (39.2)       |
| Liver fibrosis score 3–6, <i>n</i> (%)           | 17 (60.8)       |
| Liver histopathological assessment:              |                 |
| Histological activity index, mean $\pm$ SD       | 5.36 $\pm$ 2.40 |
| Liver fibrosis score, mean $\pm$ SD              | 1.48 $\pm$ 1.09 |

**Table II.** Comparison of pre- and post-treatment in all patients with laboratory values

| Parameter                         | Group 1<br>Pre-treatment<br>(n = 28)<br>(mean ± SD) | Group 2<br>Post-treatment<br>(n = 28)<br>(mean ± SD) | P-value  |
|-----------------------------------|---|--|----------|
| Alanine transaminase [IU/l]       | 47.47 ±31.63  | 26.40 ±20.63   | 0.001    |
| Aspartate transaminase [IU/l]     | 45.88 ±28.60  | 27.85 ±15.47   | < 0.0001 |
| Alkaline phosphatase [IU/l]       | 73.77 ±20.12  | 75.92 ±20.11   | 0.618    |
| Gamma-glutamyl transferase [IU/l] | 40.59 ±27.78  | 26.11 ±12.51   | 0.005    |
| Total bilirubin [mg/dl]           | 0.93 ±0.32  | 0.82 ±0.39   | 0.216    |
| Direct bilirubin [mg/dl]          | 0.21 ±0.11  | 0.18 ±0.12   | 0.175    |
| HCV-RNA [ $\times 10^6$ IU/ml]    | 49.61 ±5.03   | 7.55 ±1.27   | 0.011    |
| Prothrombin time [s]              | 11.50 ±1.39   | –  | –        |
| Albumin [g/dl]                    | 3.87 ±0.40  | –  | –        |
| $\alpha$ -Fetoprotein [IU/ml]     | 4.09 ±3.26  | 2.65 ±1.59   | 0.001    |

**Table III.** Pre-treatment and control group to compare the value of laboratory parameters

| Parameter                     | Group 1<br>(pre-treatment)<br>(n = 28)<br>(mean ± SD) | Controls<br>(n = 28)<br>(mean ± SD) | P-value  |
|-------------------------------|---|-------------------------------------|----------|
| Haemoglobin [g/dl]            | 14.66 ±2.00   | 13.66 ±1.66                         | 0.054    |
| Leucocyte [ $\times 10^9$ /l] | 7.44 ±2.63  | 7.05 ±1.62                          | 0.700    |
| Platelet [ $\times 10^9$ /l]  | 198.28 ±60.92   | 258.00 ±44.88                       | < 0.0001 |
| Mean platelet volume [fl]     | 8.89 ±1.20  | 8.21 ±1.18                          | 0.045    |

**Table IV.** Post-treatment and control group to compare the value of laboratory parameters

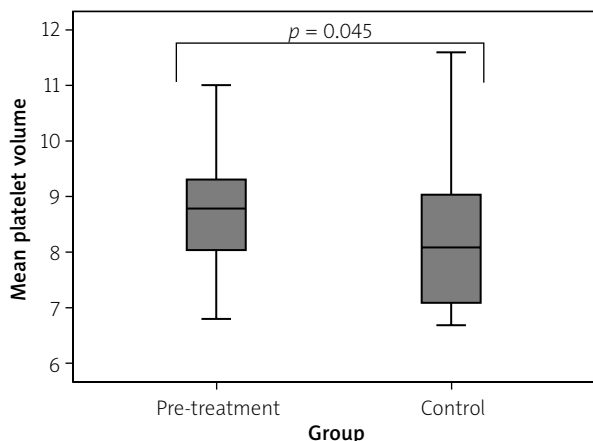
| Parameter                     | Group 2<br>(post-treatment)<br>(n = 28)<br>(mean ± SD) | Control<br>(n = 28)<br>(mean ± SD) | P-value  |
|-------------------------------|--|------------------------------------|----------|
| Haemoglobin [g/dl]            | 13.98 ±1.83  | 13.66 ±1.66                        | 0.438    |
| Leucocyte [ $\times 10^9$ /l] | 5.61 ±1.75   | 7.05 ±1.62                         | 0.003    |
| Platelet [ $\times 10^9$ /l]  | 195.35 ±65.64  | 258.00 ±44.88                      | < 0.0001 |
| Mean platelet volume [fl]     | 8.00 ±1.07   | 8.21 ±1.18                         | 0.455    |

All data mean ± SD.

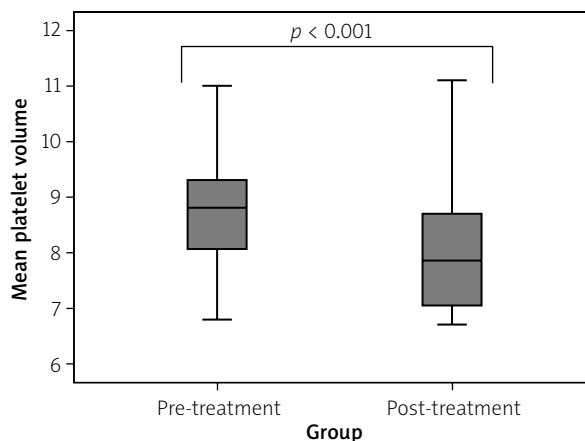
assessment of the abdominal ultrasound images revealed no statistically significant difference in the MPV values between the patients with and without grade 1 hepatic steatosis (8.87 ±1.65 and 8.90 ±0.96, respectively;  $p = 0.693$ ). The pre-treatment MPV values were not statistically significant between the patients who did and did not achieve complete treatment response (8.83 ±1.25 and 8.93 ±1.20, respectively;  $p = 0.561$ ). There were statistically significant differences in the pre- and

post-treatment MPV values between the patients who did and did not achieve complete treatment response ( $p = 0.034$  and  $p < 0.001$ , respectively) (Table V).

The pre-treatment histopathology assessment demonstrated no correlation between HAI, LFS, and MPV. The MPV did not show a statistically significant difference between the patients with low-grade and high-grade fibrosis (8.75 ±1.24 and 9.10 ±1.16, respectively;  $p = 0.480$ ).



**Figure 1.** There are statistically significant differences between baseline MPV values and the control group



**Figure 2.** There are statistically significant differences between pre-treatment MPV values and the post-treatment group

### Discussion

In our study, we have shown that pre-treatment MPV values were higher in CHC patients compared to post-treatment values, and that they were also higher compared to values in the control group. There were no differences between the post-treatment MPV value and the values in the control group. The complex effects of hepatitis C on the liver have not been elucidated completely. Considering the controlling impact of the liver on the immune system, it directly or indirectly leads to local and systemic inflammation. As a result of the systemic inflammation, the effect on the precursor platelet cells in the bone marrow results in changes in MPV [5, 16].

The MPV shows variability between the presence of low-grade and high-grade inflammation. Recently, increased levels of MPV were demonstrated in many diseases [17], most of these are related to endothelial dysfunction on the basis of inflammation [18]. The higher MPV values are also considered to be a useful indicator of higher thrombocyte activity. The level of platelets is increased in cases of high-grade inflammation, leading to a reduction in the MPV level as a result of the migration of the majority of the large reactive platelets to inflammatory sites and intensive consumption of these platelets [6, 7]. In the case of low-grade inflammation, an increase in the MPV level occurs as a result of the increased reactive immature platelets. Some studies reported that MPV were higher in patients with non-alcoholic fatty liver disease (NAFLD) [19], chronic hepatitis B (CHB) [12], and CHC [13]. Many noninvasive tests have been studied for diagnosis and determination of the LFS.

Non-alcoholic fatty liver disease is a chronic inflammatory disease with a pathogenesis involving oxidative stress and pro-inflammatory cytokines, which may lead

**Table V.** Pre- and post-treatment MPV levels in relation to treatment response

| MPV                     | Pre-treatment (mean ± SD) | Post-treatment (mean ± SD) | P-value |
|-------------------------|---------------------------|----------------------------|---------|
| MPV in SVR (n = 12)     | 8.83 ± 1.25               | 8.14 ± 1.16                | 0.034   |
| MPV in non-SVR (n = 16) | 8.93 ± 1.20               | 7.89 ± 1.03                | 0.001   |

MPV – mean platelet volume, SVR – sustained virological response.

to non-alcoholic hepatic steatosis (NASH), fibrosis, and cirrhosis. Alkhoury *et al.* [10] demonstrated high MPV levels in NASH patients compared to steatosis patients, and patients with steatosis had higher MPV levels compared to those with a normal biopsy result. Celikbilek *et al.* [19] reported higher MPV levels in NAFLD patients relative to control subjects.

Chronic hepatitis B infection, like the CHC infection, is among the significant viral infections that can lead to chronic liver disease. It may result in liver inflammation, cirrhosis, and HCC. An increase in the MPV level occurs together with an increase in the production of immature platelets in the bone marrow in the case of CHB infection [12, 14, 20]. Turhan *et al.* [20] reported higher MPV in inactive CHB patients relative to healthy individuals. Ekiz *et al.* [12] demonstrated that high MPV levels were statistically significantly higher in CHB patients compared to the control group. They also showed that MPV was observed to be higher in patients with severe fibrosis relative to those without marked fibrosis. Ceylan *et al.* [14] showed no statistically significant difference in MPV level between the CHB patients with a liver fibrosis score of 0 to 2 and a LFS of 3 to 6. The MPV may provide useful information to predict the degree of liver inflammation along with other markers [14].

Considering the effects of pro-inflammatory cytokines on platelet production and activation, studies in CHC patients mostly investigate the cytokine level. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) are among the progenitor cytokines that affect platelet production [6, 7, 16]. In the case of chronic liver disease, IL-6 production associated with secondary inflammation during the process of fibrosis and immature platelets are considered to increase the MPV level, suggesting a correlation with the grade of fibrosis [6, 12, 16]. Previous studies have shown that MPV levels were increased in CHC with inflammation and advanced fibrosis. Calculation of MPV along with the use of other markers may give further information about liver fibrosis severity in CHC [13]. Purnak *et al.* [13] reported statistically significantly higher MPV levels in patients relative to the control subjects. MPV was higher in patients with advanced fibrosis compared to those with mild fibrosis.

Proteins associated with hepatitis C infection stimulate the release of the pro-inflammatory cytokines. They are also increased in various types of chronic liver disease, including CHC. These cytokines are significantly involved in inflammation, regeneration, and fibrosis in the liver, and have an impact on the disease progression [16, 21]. Ueyama *et al.* [22] reported statistically significantly higher IL-6 levels in CHC patients relative to the control subjects. Huang *et al.* [23] demonstrated that serum IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels are elevated in patients with HCV-related liver diseases, especially in liver cirrhosis. These levels reflect hepatic dysfunction better than liver inflammation parameters, which might explain the higher serum concentrations of cytokines in liver cirrhosis patients. In another study, Ivashkin *et al.* [24] reported a reduction in post-treatment TNF- $\alpha$  levels relative to the pre-treatment values in CHC patients. Peg-IFN and RBV therapy provides a reduction in local and/or systemic inflammation due to the regression of necro-inflammation and liver injury in CHC patients.

These above studies have shown that some inflammatory markers affecting platelet function may be changed after standard therapy in patients with CHC. Consequently, we aimed to investigate the MPV levels as platelet activity markers after standard therapy in patients with CHC. We reported that there were statistically significant differences of MPV values before and after standard therapy. This study has some limitations; they include the small number of patients, the retrospective nature of the study, the fact that the correlation between the cytokine levels and MPV was not investigated, and the absence of assessment of histopathology investigations on post-treatment liver biopsies.

## Conclusions

We suggest that MPV is a simple and an inexpensive marker that may be used in assessing low-grade chronic inflammation in patients with CHC. Further prospective randomised studies are needed to elucidate the significance of MPV for CHC patients.

## Conflict of interest

The authors declare no conflict of interest.

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