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# Mean platelet volume is a useful indicator of systemic inflammation in cirrhotic patients with ascitic fluid infection

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**ABSTRACT**

**Aim.** Ascitic fluid infection (AFI) consists primarily of two variants, namely, culture-negative neutrocytic ascites and spontaneous bacterial peritonitis (SBP). Mean platelet volume (MPV) has begun to be used as a simple and inexpensive indicator of inflammation in some diseases. We aimed to analyse whether platelet size alterations would be useful in predicting AFI in cirrhotic patients. **Material and methods.** A total of 135 patients with ascites due to cirrhosis and 55 control subjects were enrolled in this study. According to ascitic fluid analysis, 58 patients were considered to have AFI. MPV and inflammatory parameter values were determined for all study participants. The ability of MPV values to predict AFI in cirrhotic patients was analysed using receiver operator characteristic (ROC) curve analysis. **Results.** A statistically significant increase in MPV levels was observed in cirrhotic patients with AFI compared to cirrhotic patients without AFI and healthy controls ($p < 0.001$). A statistically significant increase was observed in the AFI group with respect to MPV, C-reactive protein (CRP) and white blood cell (WBC) levels. ROC curve analysis suggested that the optimum MPV level cut-off point for cirrhotic patients with AFI was 8.45, with a sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of 70.7%, 67.5%, 75.4% and 62.1%, respectively (area under curve: 0.768). **Conclusion.** Our study shows that MPV is increased in cirrhotic patients with AFI. MPV measurement can considered to be an accurate diagnostic test in predicting AFI, possibly due to an ongoing systemic inflammatory response.

**Key words.** Ascitic fluid infection. Spontaneous bacterial peritonitis. Mean platelet volume. Cirrhosis. Inflammation.

## INTRODUCTION

Patients with cirrhosis are usually prone to developing bacterial infections, primarily ascitic fluid infection (AFI), which is present in 15-25% of patients with cirrhosis and ascites.[1-3] It is a frequent and serious complication of cirrhotic ascites, and was first described by Conn HO in the mid-1960s.[4] It occurs in the absence of an intra-abdominal inflammatory focus, such as acute pancreatitis, cholecystitis, or abscess.[5] For the diagnosis of AFI, polymorphonuclear (PMN) cell count of the ascitic fluid that is obtained by paracentesis must be $\geq 250/mm^3$. From bacteriological cultures, only one germ must be isolated. Negative bacterial culture does not rule out AFI diagnosis.[6-10] AFI consists of culture-negative neutrocytic ascites (CNNA) and spontaneous bacterial peritonitis (SBP) regarding to bacterial culture results. Although AFI with positive culture results suggests a possible diagnosis of SBP, patients having diagnostic criteria for SBP but negative culture results would be suspected of CNNA.

Current literature data suggests that ascitic fluid analysis by paracentesis must be done for all patients with ascites that are admitted to the hospital.[11] Empiric antibiotic therapy should also be considered in patients with elevated PMN counts in ascitic fluid analyses. Nevertheless, a prompt result of ascitic fluid cell count is not always possible in a practical setting. Moreover, ascitic fluid culture results always take several days to one week, which suggests that they cannot be used as a screening tool. For this reason, the adjunctive use of additional markers that are non-invasive, rapid and easily

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applicable may add significant benefit for predicting the development of AFI and achieving diagnostic accuracy.

Circulating platelets are an abundant source of prothrombotic agents closely associated with inflammatory markers, and play a key role in the initiation and propagation of vascular and inflammatory diseases.[12,13] Platelets are anucleate cells and their size mostly depends on the degree of fragmentation of megakaryocytes. Platelets with increased size have a greater content of granules and can therefore exert their hemostatic and pro-inflammatory actions with greater efficiency.[14] For this reason mean platelet volume (MPV) is proposed to be an indicator of platelet function and activation. MPV is generated by full blood count analyzers as part of the complete blood count (CBC) test cycle.[15] Some studies have reported that MPV increases in myocardial infarction, cerebrovascular disease, Alzheimer's disease, hypertension, and celiac disease.[12,16-19] In contrast, it has been reported that MPV decreases in active inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and acute pancreatitis.[15,20,21] It has been suggested that the dual role of this marker is largely influenced by the intensity of inflammation.[22] Although MPV is well studied in a number of prospective studies in different populations of patients, no literature data exists showing the role of MPV in cirrhotic patients. In this respect, the present study was undertaken in order to investigate whether MPV is useful for determining the systemic inflammatory response in AFI. Moreover, we have analyzed the overall accuracy of MPV in patients with AFI and compared it with other inflammatory markers.

## MATERIAL AND METHODS

For this study, a retrospective review was carried out of the available medical records of patients with ascites due to cirrhosis who were admitted to Turkiye Yuksek Ihtisas Training and Research Hospital from February 2008 to September 2011. Biochemical and hematological investigations, in addition to microbiological cultures of the ascitic fluid, were routinely performed for all patients. Severity of the underlying liver disease was assessed using the child pugh score (CPS) classification.

Paracentesis of ascitic fluid was performed for every patient with cirrhosis and ascites that was admitted to our clinic, independently of the clinical suspicion of AFI, as a routine procedure. AFI diagnosis was based on the presence of ≥ 250 cells/mL PMN in the ascitic fluid, with or without positive ascitic fluid culture in the absence of a hemorrhagic ascites of secondary peritonitis. The following data were extracted from the hospital medical records, including patient age, gender, etiology of liver disease, hepatic function status (as determined by CPS), and laboratory tests at the onset of clinical symptoms with positive ascitic fluid analysis.

All CBC analysis was performed in the hematology laboratory of our hospital. CBC analyses were performed with the same analyzer within 2 hours after collection of blood samples with the use of a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer. Platelet number, MPV and platelet distribution width (PDW) were also recorded for all patients with ascites.

Exclusion criteria included patients who were immunocompromised and patients who had received antibiotic prior to hospital admission. Moreover, patients with heart failure, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, hematological disorders and neoplastic disorders were also excluded from this study. None of the study participants had received anticoagulant medications, non-steroidal anti-inflammatory drugs (NSAID) or oral contraceptive drugs before hospital admission.

The control group consisted of 55 healthy age and gender-matched subjects (male/female: 23/32). None of the controls included in this study had a history of diabetes mellitus, hyperlipidemia, hypertension or any other co-morbid illnesses. The study was conducted in accordance with the guidelines of the Helsinki declaration

### Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 18 software (SPSS Inc., Chicago, IL, United States). Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Values are presented as mean ± standard deviation or in the case of non-normally distributed data, as median and range. Comparisons of percentages between different groups of patients were carried out using the chi-squared test. All normally-distributed data were analyzed using Independent Samples T Test. Data found to be non-normally distributed were analyzed using the Mann-Whitney U test. One-Way ANOVA was used to compare normally distributed variables in three groups. Levene test was used to assess the homogeneity of variances. *Post-hoc* Tukey or

Tamhane's T2 tests were used according to homogeneity of variances. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of MPV, PDW, CRP, ESR and WBC with maximum sensitivity and specificity for differentiation of cirrhotic patients with AFI from those without AFI. Spearman's correlation analysis was done between MPV levels and other inflammation markers. A p-value of $< 0.05$ was deemed statistically significant.

## RESULTS

One hundred thirty-five patients with ascites due to cirrhosis and 55 control subjects were enrolled in the present study. Cirrhotic patients consisted of 88 (65.2%) men and 47 (34.8%) women, whereas the control group consisted of 23 (40.4%) men and 32 (56.1%) women. There were no statistically significant differences between the ages of the study participants. With respect to the etiology of the underlying hepatic disease, 82 patients (60.7%) had virus related cirrhosis, 18 (13.3%) had alcoholic cirrhosis, 20 patients (14.8%) had cryptogenic and 15 (11.1%) patients with other causes of cirrhosis (metabolic, toxic, autoimmune, biliary and non-alcoholic steatohepatitis related). According to the CPS, 54 (40%) of the patients were classified as stage B and 81 (60%) of the patients were classified as stage C. Cirrhotic patients with AFI were also classified according to their CPS (34.5% stage B and 65.5% stage C). Clinical and laboratory characteristics of the study participants are shown in table 1.

A *post-hoc* analysis revealed a significant difference between MPV levels of cirrhotic patients with AFI compared to cirrhotic patients without AFI ($p < 0.001$) and healthy controls ($p < 0.001$) (8.79 ± 1.01 fL, 8.05 ± 0.83 fL and 7.88 ± 0.47 fL, respectively) (Figure 1). No statistically significant difference was observed between cirrhotic patients without AFI and healthy controls ($p = 0.368$). In patients with AFI, a further analysis with respect to MPV levels was done between patients with SBP and CNNA. No statistically significant difference was observed between patients with SBP and CNNA (8.70 ± 0.86 fL and 8.86 ± 1.12 fL, respectively).

According to ascitic fluid analysis, 58 patients (M/F: 37/21) were defined as having AFI (mean age 57.9 ± 13.9 years) and 77 patients (M/F: 51/26) were defined as patients without AFI (mean age 58.7 ± 14.4 years). Although a statistically significant increase with respect to MPV, CRP and WBC levels was observed in the AFI group, no significant difference was observed with respect to PDW and ESR levels. A comparison of MPV and PDW with other inflammation markers in both of these groups is shown in table 2.

A receiver operator characteristic (ROC) curve analysis suggested that the optimum MPV level

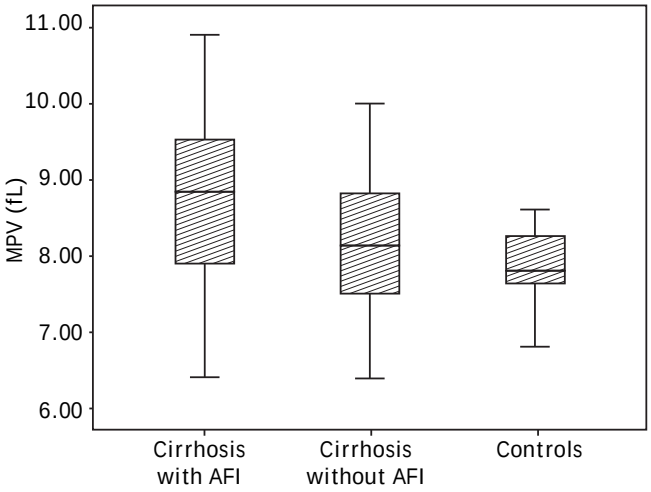


***Figure 1.*** *Boxplot presentation of MPV levels of the cirrhosis patients with or without ascitic fluid infection (AFI) and healthy controls.*

**Table 1.** Demographic features and laboratory values of study participants.

| | Patients with cirrhosis (n:135) | Control group (n:55) | p |
|---|---|---|---|
| Gender (F/M) | 47/88 | 32/23 | 0.003 |
| Age (year) | 58.1± 14.1 | 53.7±13.9 | NS* |
| Hemoglobin (g/dL) | 10.3± 1.7 | 14.4±1.2 | < 0.001 |
| WBC ($mm^3 \times 10^3$) | 6.7(1.2 - 23.5) | 7.1(3.2 - 10.4) | NS* |
| Platelet ($mm^3 \times 10^3$) | 108(19 - 377) | 265(163 - 417) | < 0.001 |
| MPV (fL) | 8.37 ±0.98 | 7.88±0.47 | < 0.001 |
| PDW (%) | 17.4 (15.6 - 53.6) | 16.6 (16.1 - 43.7) | NS* |
| CP-score (A/B/C) | 0 /54/ 81 | | |

*NS: Not significant. Data are presented as median (range) or mean (SD).

cut-off points for cirrhotic patients with AFI was 8.45 fL, with a sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of 70.7%, 67.5%, 75.4% and 62.1%, respectively (area under curve: 0.768) (Figure 2). Overall accuracy of MPV in determination of AFI was 68.8%. The same analysis for MPV and other inflammation markers is shown in table 3. Patients with

**Table 2.** Comparison of MPV and PDW with other inflammation markers in patients with cirrhosis with or without SBP

| | Cirrhosis with AFI (n:58) | Cirrhosis without AFI (n: 77) | p |
|---|---|---|---|
| MPV (fL) | 8.79 ± 1.01 | 8.05 ± 0.83 | < 0.001 |
| PDW (%) | 17.6 (15.6-53.6) | 17.4 (15.8-48) | NS* |
| CRP (mg/L) | 12.8 (2-67) | 5.2 (0.3-41) | < 0.001 |
| WBC ($mm^3x10^3$) | 8.3 (1.2-23.5) | 5.6 (1.7-15) | < 0.001 |
| ESR (mm/h) | 34 (3-110) | 25 (3-110) | NS* |

*NS: Not significant, Data are presented as median (range) or mean (SD). MPV: Mean platelet volume. PDW: Platelet distrubition width. CRP: C reactive protein. WBC: White blood cell, ESR: Erythrocyte sedimentation rate.

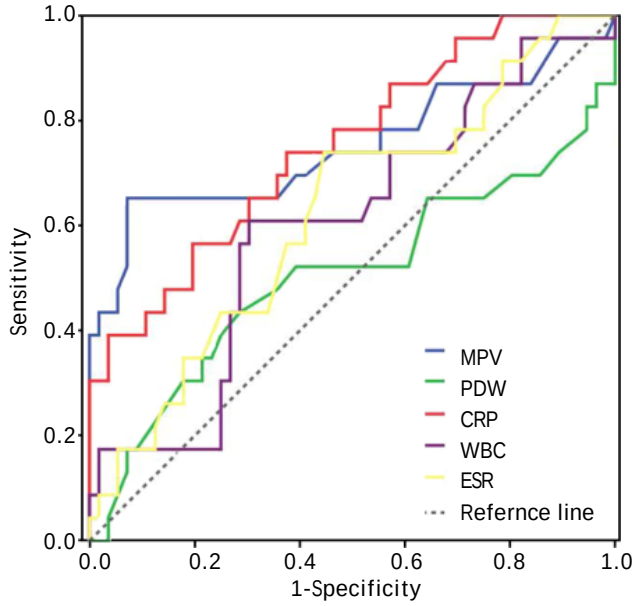


***Figure 2.*** *Receiver operating characteristic (ROC) curves of MPV and other inflammation markers in detecting ascitic fluid infection in cirrhotic patients.*

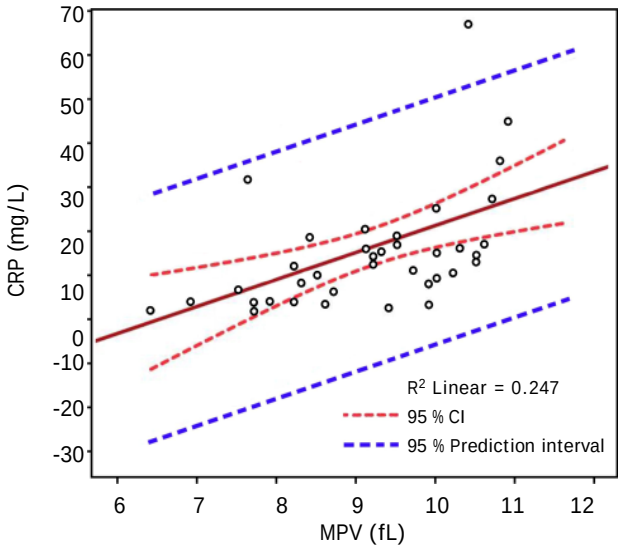


***Figure 3.*** *The correlation between MPV and CRP in cirrhotic patients with ascitic fluid infection. Lines representing the 95% confidence interval (CI) and the 95% prediction interval of the regression line (spearman's rank correlation coefficient r = 0.535 p ≤ 0.001).*

**Table 3.** Overall accuracy and ROC analyses of MPV and other inflammation markers to differentiate cirrhotic patients with AFI from cirrhotic patients without AFI.

| | AUC | Sensitivity (%) | Specificity (%) | NPV (%) | PPV (%) | Overall accuracy |
|---|---|---|---|---|---|---|
| MPV (Cut off:8.45) | 0.768 | 70.7 | 67.5 | 75.4 | 62.1 | 68.8 |
| PDW (Cut off:17.45) | 0.5 | 52.4 | 51.7 | 60.8 | 43.1 | 51.9 |
| CRP (Cut off:9.15) | 0.749 | 68.6 | 65.7 | 80.7 | 50 | 66.6 |
| WBC (Cut off:6980) | 0.705 | 67.2 | 66.2 | 72.9 | 60 | 66.6 |
| ESR (Cut off:29.5) | 0.572 | 59 | 56.3 | 71.4 | 42.6 | 57.2 |

AFI: Ascitic fluid infection. MPV: Mean platelet volume. PDW: Platelet distrubition width. CRP: C reactive protein. ESR: Erythrocyte sedimentation rate. WBC: White blood cell. AUC: Area under curve. PPV: Positive predictive value. NPV: Negative predictive value.

AFI were analyzed according to CPS. No significant difference with respect to MPV levels was observed between CPS stage B and C (p: 0.949).

Although spearman correlation analysis showed that there was a significant correlation between MPV and CRP ($r = 0.535$, $p \leq 0.001$) (Figure 3), no correlation was observed with WBC ($r = 0.049$, $p = 0.714$), ESR ($r = 0.105$, $p = 0.524$) and PDW ($r = 0.194$, $p = 0.218$).

## DISCUSSION

In the present study, mean platelet volume was significantly increased in cirrhotic patients with AFI compared with cirrhotic patients without AFI and the control group [$p < 0.001$ (Figure 1)]. The overall accuracy of MPV for detecting AFI was found to be comparable to CRP and WBC and superior to ESR. No significant correlation was found between MPV levels in AFI patients according to CPS.

AFI is a common and severe complication of patients with cirrhotic ascites.[23] It is defined as an infection of initially sterile ascitic fluid without a detectable and surgically treatable source of infection.[6] In this respect, SBP as a main reorganized entity of AFI, has been defined as an AFI with growth of bacteria in the culture of ascitic fluid. AFI prevelance among hospitalized cirrhotic patients varies between 10 and 30%. Despite early initiation of antibiotic therapy, which may result in a satisfactory response in most cases, the mortality still remains considerably high at 30-50%.[24-26] For this reason, early determination of inflammatory activity has a crucial role for the assessment of AFI and for therapeutic modifications. Although underlying hepatic disorder, systemic complaints of the patients and ascitic fluid analyses are the cornerstones of the diagnosis, several invasive/non-invasive methods have also been studied for assessing AFI in cirrhotic patients. Diagnostic paracentesis, which is considered to be the gold standard for diagnosing AFI, is sometimes associated with minor complications (e.g. bleeding, visceral perforation, local infection and persistent leakage after paracentesis). Therefore, a simple, easy applicable, rapid and inexpensive diagnostic test to make a presumptive diagnosis of AFI in cirrhotic patients would help clinicians to reach these goals.

The use of additional diagnostic tools, such as leucocyte esterase reagent strips, pH testing, and lactoferrin in ascitic fluid are also considered to be helpful in SBP diagnosis.[27] Moreover, a recent report by Gundling, *et al.*[2] in which the role of fecal calprotectin (FC) in diagnosing the onset and severity of hepatic encephalopathy and SBP were assessed, demonstrated that FC concentrations may serve as a screening tool for SBP. Another study focused on the diagnostic role of plasma and ascitic fluid procalcitonin for estimating SBP diagnosis was reported by Spahr *et al.*[28] Procalcitonin in plasma, but not in ascites, was found to be significantly higher in patients with SBP compared with controls ($0.74 \pm 0.6$ *vs.* $0.2 \pm 0.1$ ng/mL, $p < 0.05$). Although several additional markers were also proposed for estimating systemic inflammation in patients with AFI, the role of platelets as a marker of systemic inflammation has not yet been clearly elucidated. In this respect, the primary aim of the present study was to evaluate platelet number and size alterations in cirrhotic patients with or without AFI in correlation with other inflammation markers and clinical severity indices. To the best of our knowledge, this issue has not been previously investigated. For this reason, we think that our preliminary results will shed further light on the complex relationship between systemic inflammation and platelet size alterations.

MPV is one of the most widely used surrogate markers of platelet activation, in which larger platelet volume means both an enzymatically and metabolically more active platelet compared to a smaller one.[22,29] MPV has been shown to reflect the inflammatory burden and disease activity in several diseases, including rheumatoid arthritis, celiac disease, acute pancreatitis, inflammatory bowel diseases, myocardial infarction, Alzheimer's disease and acute ischemic stroke.[15-17,19,21,22,30] Although conflicting results exist in the literature that link both increased and decreased MPV to inflammation, evidence particularly derived from prospective trials proposes an increase in MPV with a risk of thrombosis and low grade inflammatory conditions. High grade inflammatory conditions, such as active rheumatoid arthritis and ulcerative colitis, are commonly reported to be present with low MPV levels.[20,21,31,32] Since the AFI in cirrhotic patients commonly results in a systemic inflammatory response, we hypothesized that MPV would be affected during the disease course. If such an association is discovered, MPV might be helpful in diagnosing patients with AFI earlier in the course of disease progression, which may result in better patient outcome. In this report, a significant increase in MPV levels in cirrhotic patients with AFI was discovered. Moreover, a positive correlation between MPV and other systemic inflammatory markers supported our initial hypothesis that MPV could reflect ongoing systemic inflamma-

tory responses in cirrhotic patients with AFI. Based on our findings, it is reasonable to suggest that MPV not only represents platelet activation, but also systemic inflammation and infection.

Although there is no ideal single serum inflammation marker for diagnosing AFI, C-reactive protein (CRP) is a helpful diagnostic test in reflecting systemic inflammation in cirrhotic patients. Although the exact in vivo functions of CRP during inflammation is still a matter of debate, there is a growing body of evidence revealing its particular role in both recognizing and eliminating foreign pathogens.[33] Being an acute phase reactant, CRP binds to different substrates and stimulates the complement system, has a crucial role in cytokine secretion and increases the phagocytosis of leukocytes. In a study by Yildirim, *et al.*,[34] it was found that CRP was increased in the serum and ascitic fluid of SBP patients. The sensitivity and specificity of ascitic fluid CRP (cut-off value >1.0 mg/dL) in discriminating infected ascites from sterile ascites were 90% and 76%, respectively. Similarly, Spahr, *et al.*[28] reported that CRP concentrations were higher in plasma in patients with SBP compared to controls (85.3 ± 63 *vs.* 18.6 ± 19 mg/dL, $p < 0.05$, respectively). In the present study, the overall accuracy of CRP was 66.6% with a sensitivity, specificity, NPV and PPV of 68.6%, 65.7%, 80.7% and 50% (AUC:0.749).

The role of PDW as an index for platelet activation was also investigated in this study. PDW is a measure of the variation of red blood cells, which can be an indicator of platelet activation, and thus be related to inflammatory processes during the development of AFI. In this study, no statistically significant difference was found between cirrhotic patients with or without AFI and controls with respect to PDW levels. Moreover, PDW levels did not differ in patients with AFI with respect to CPS.

In conclusion, this study for the first time has demonstrated that MPV is significantly elevated in cirrhotic patients with AFI, independent from the severity of liver disease that is reflected by CPS. Moreover, our results suggest that subjects with AFI are susceptible to increased platelet activation and increased MPV values that contribute to systemic inflammatory responses. We therefore propose that MPV, as a cheap, rapid and easily applicable test, is a valuable diagnostic tool for a rapid assessment of AFI diagnosis in cirrhotic patients. Further studies with larger numbers of patients are warranted to ascertain associations of MPV levels with diverse markers of inflammation and disease activity.

## CONFLICT OF INTEREST

Authors declare no conflict of interest related to this article.

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