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## SHORT COMMUNICATION

# Markedly Increased Mean Platelet Volume in Bacterial Meningitis

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**SUMMARY**

***Background:*** **Differentiating bacterial and viral meningitis is crucial, and this study explored the potential of mean platelet volume (MPV) as a marker for differentiation.**
***Methods:*** **Blood samples were collected from patients with central nerve system related manifestations, and MPV was tested. Cerebrospinal fluid samples were obtained and bacterial culture and the FilmArray ME panel were performed. The distribution of MPV was compared between groups.**
***Results:*** **The study included 8 patients in the bacterial meningitis group and 12 patients in the viral meningitis group. The bacterial meningitis group showed a significantly higher median MPV of 10.9 (9.2 - 11.6) fL compared to the viral meningitis group with 8.4 (8.1 - 8.8) fL ($p < 0.0001$).**
***Conclusions:*** **MPV could serve as a diagnostic indicator to differentiate between bacterial and viral meningitis. Larger studies are needed to validate these findings.**
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**KEYWORDS**

bacterial meningitis, viral meningitis, mean platelet volume, cerebrospinal fluid, FilmArray ME panel

## INTRODUCTION

Bacterial meningitis is a severe, life-threatening condition of the subarachnoid space and meninges due to bacterial infection. Meningeal inflammation can cause thrombosis of cerebral arterioles, arteries, and cerebral vein [1]. Platelets play an essential role in thromboembolic and inflammatory mechanisms [2-4]. Mean platelet volume (MPV) is a platelet index measured routinely in a complete blood count (CBC) using automated analyzers [5,6]. The MPV is a platelet size index that reflects platelet activation and function [5]. However, it has not been fully investigated in bacterial meningitis. Furthermore, bacterial and viral meningitis have similar symptoms, making differentiation crucial. To differentiate between bacterial and viral meningitis, cerebrospinal fluid (CSF) cell counts, Gram staining, and chemistry tests, such as protein and glucose tests, are conducted. While these tests can be helpful in distinguishing between the two conditions, they are nonspecific and can be influenced by other factors. Therefore, in this study,

we investigated MPV in bacterial meningitis and explored whether the distribution of MPV in bacterial meningitis differed from viral meningitis to determine the potential utility of MPV as an adjunctive marker.

## MATERIALS AND METHODS

Blood was collected in EDTA-containing tubes and MPV was tested within 2 hours of blood collection using an Advia 2120 (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). From February 2021 to April 2023, the study enrolled adult patients with CNS-related manifestations, underwent neurological examination by a neurologist, and had their CSF collected and sent to the laboratory for pathogen detection. The patients were diagnosed with infectious meningitis based on positive findings from culture and/or polymerase chain reaction (PCR) tests. The patients with contaminated diagnostic testing results as determined by the attending physician, with a pre-existing history of chronic inflammatory disease or hematologic disease, without MPV results, initially diagnosed with sepsis or pneumonia, taking anticoagulants or antiplatelet medications, and underwent neurosurgical procedures or had CSF samples collected through external ventricular drainage were excluded from the study. CSF samples were collected from the patients and tests, including bacterial culture, white cell count, protein, glucose, and the FilmArray ME panels (BioMerieux, Salt Lake City, UT, USA) were conducted. The bacterial colonies obtained were identified using MALDI-TOF MS (Bruker Daltonics, Bremen, Germany). MPV values were collected from patients on the day before, the day of, and the day after obtaining CSF samples. The distribution of MPV between two groups was compared using the Mann-Whitney U test and the diagnostic performance of MPV in differentiating bacterial meningitis from viral meningitis was evaluated using receiver operating characteristic (ROC) curve analysis at 95% confidence interval. The statistical analyses were performed using MedCalc v 20.109 (MedCalc Software, Mariakerke, Belgium) and MS Excel 2016 (Microsoft, Redmond, WA, USA) software packages. The statistical significance was set at $p < 0.05$.

## RESULTS

A total of 1,943 CSF cultures were requested with 177 (9.1%) positive samples. Among them, 166 samples obtained after neurosurgical procedures were excluded. After excluding three additional samples based on these criteria, eight samples were obtained from seven patients. Among them, three patients had *S. pneumoniae* cultured from their CSF, and *Streptococcus gallolitic*us, *Streptococcus constellatus*, and *Stenotrophomonas maltophilia* were cultured in 3 patients each. In one patient, both *S. maltophilia* and *Enterococcus faecium* were cultured. The FilmArray ME panel also detected bacteria in three samples with *Escherichia coli* identified in one sample, which was classified as a false positive by the attending physician. Another sample was positive for *S. pneumoniae* in both the culture and Film Array ME panel. The remaining sample, which tested positive for *E. coli*, was included in the bacterial meningitis group. Finally, 8 patients were enrolled in the bacterial meningitis group.

During the study period, a total of 248 CSF samples underwent FilmArray ME panel testing, of which 13 (5.2%) were detected with viruses. Of the 13 samples with viruses, one was excluded because of the absence of MPV results. Therefore, the remaining 12 samples were categorized under the viral meningitis group, where varicella zoster virus (VZV) was detected in five patients, herpes simplex virus 2 in three patients, herpes simplex virus 1 in two patients, human herpesvirus 6 (HHV-6) in two patients, and cytomegalovirus in one. Moreover, one patient from the viral meningitis group also showed concurrent detection of VZV and HHV-6. The MPVs for the bacterial and viral meningitis groups were 24 and 18, respectively. In addition, 143 individuals were randomly selected from the medical check-up group as the control group, which was used in our previous studies [4,5,8]. In the bacterial meningitis group, age range and male-to-female ratio were 57 - 87 years and 3:5, respectively. In the viral meningitis group, age range and male-to-female ratio were 23 - 81 years and 7:5, respectively. The characteristics of the study participants and CSF test results are summarized in Table 1. The median (interquartile range) MPV in the bacterial meningitis group was significantly higher (10.9; 9.2 - 11.6 fL) than that in the viral (8.4; 8.1 - 8.8 fL) meningitis group ($p < 0.0001$, Figure 1). The healthy control group demonstrated a significantly lower distribution (7.9; 7.6 - 8.3 fL) than the bacterial and viral meningitis groups ($p = 0.0003$). The ROC curve analysis showed a sensitivity of 72.0% (50.6 - 87.9%) and a specificity of 100.0% (85.8 - 100.0%). The area under the curve (AUC) was 0.911 (0.760 - 0.974) with cutoff criterion > 9.7 ($p < 0.0001$, Figure 2).

## DISCUSSION

In bacterial meningitis, the MPV showed a statistically significant increase and good diagnostic performance. There are many candidate mechanisms by which bacteria interact with platelets, such as direct interaction with various platelet receptors and secretion of bioactive substances [7]. Platelets express a number of surface receptors involved in platelet-bacteria interactions [10]. Platelet granules contain a broad spectrum of proteins that are released upon platelet activation, including cytokines, inflammatory mediators, and antimicrobial proteins. In addition, bacterial toxins have been suggested as potent platelet activators that cause intravascular platelet aggregation. Platelets contribute to the antibacterial activity of the host, including neutrophils, phago-

**Table 1. Overview of the characteristics and test results for the included patients.**

| | Bacterial meningitis | Viral meningitis | p-value |
|---|---|---|---|
| Male:Female | 3:5 | 7:5 | |
| Age (years) | 66 (62 - 75) | 41 (32 - 73) | 0.0587 |
| Mean platelets volume (fL) | 10.9 (9.0 - 11.6) | 8.4 (8.1 - 8.8) | < 0.0001 |
| CSF White blood cells (/mm$^3$) | 2,894 (1 - 12,434) | 186 (63 - 289) | 0.3545 |
| Neutrophil (%) | 74 (58 - 83) | 5 (2 - 18) | 0.0076 |
| Lymphocyte (%) | 9 (4 - 28) | 82 (59 - 81) | 0.0037 |
| CSF Protein (g/L) | 2.30 (0.52 - 8.32) | 0.87 (0.65 - 1.25) | 0.2472 |
| CSF Glucose (mmol/L) | 3.11 (0.56 - 6.11) | 3.55 (3.11 - 3.72) | 1.0000 |

**Continuous variables are expressed as median (interquartile range).**
**Abbreviation: CSF - Cerebrospinal Fluid.**

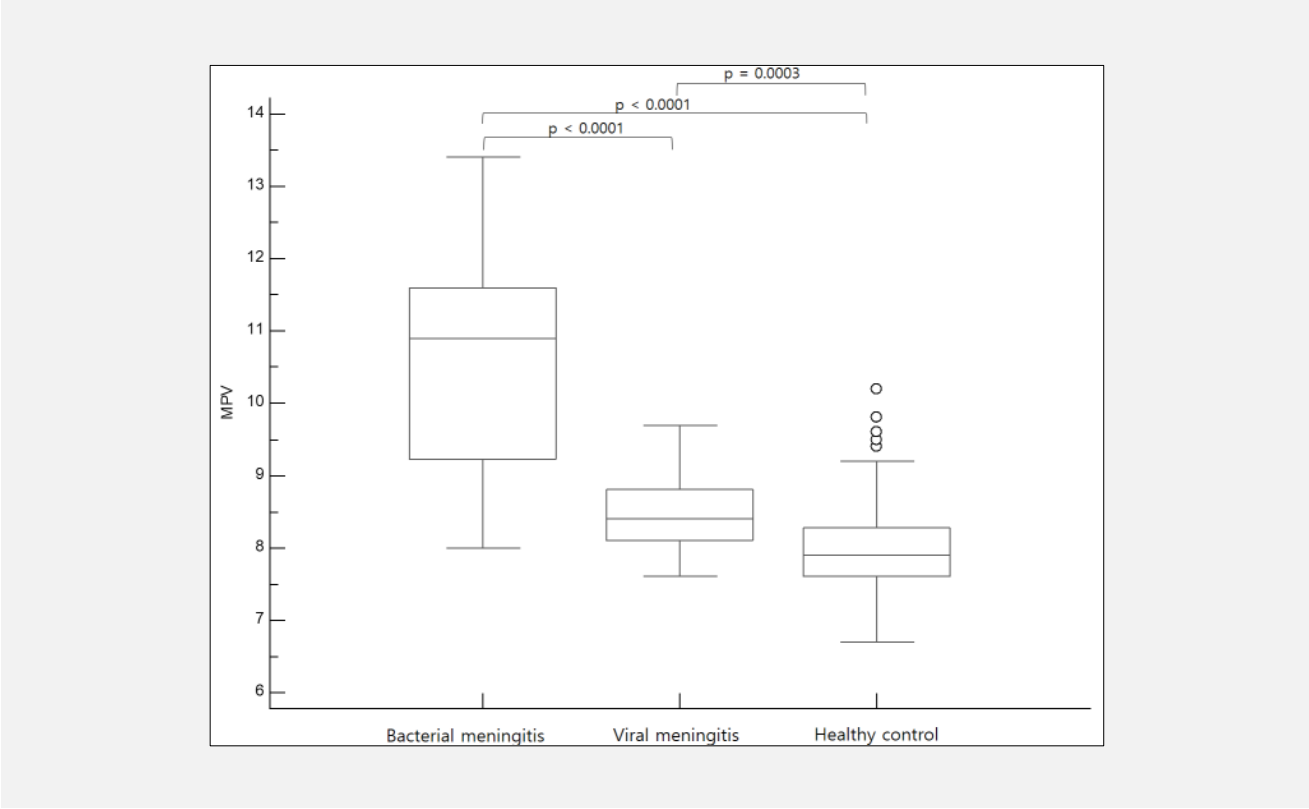


**Figure 1. Comparison of mean platelet volume (MPV) distribution among the bacterial meningitis, viral meningitis, and healthy control groups using a Box-and-Whisker plot. MPV was significantly higher in the bacterial meningitis group than in the other groups.**

cytosis, and the complement system [8]. However, there are no sufficient *in vivo* data available on identifying the essential mechanisms of platelet activation in infectious diseases, such as bacterial meningitis. Therefore, our results will contribute to the understanding of the platelet response observed in bacterial meningitis.

Molecular diagnostics are used for the differential diagnosis of infectious meningitis. The FilmArray ME panel is an automated PCR system that can detect multiple pathogens within an hour, making it useful in clinical settings [9]. However, some reports have highlighted the chance of false positives for specific pathogens,

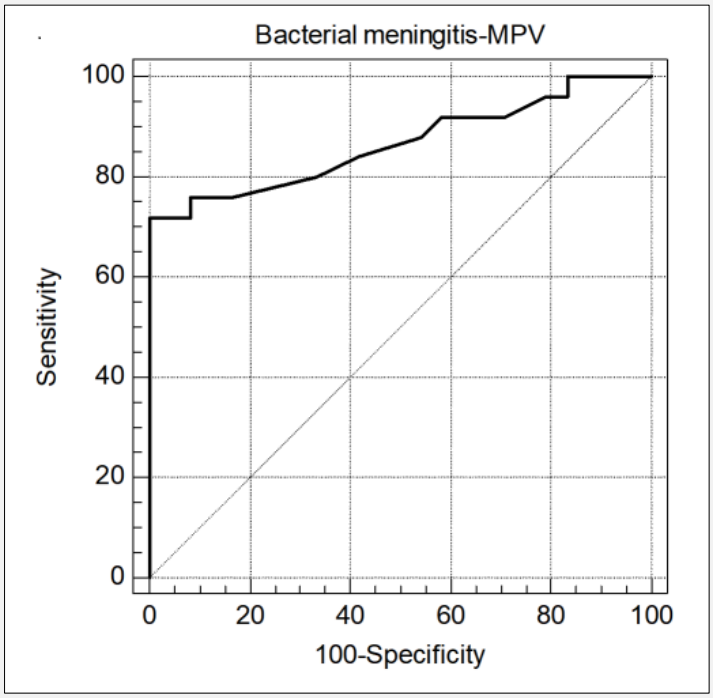


**Figure 2. Receiver operating characteristic curve analysis in this study. The mean platelet volume (MPV) presented a good diagnostic performance showing the sensitivity of 72.0% and specificity of 100%. Area under the curve was 0.911 (95% confidence interval: 0.760 - 0.974, p < 0.001) with cut-off criterion > 9.7.**

such as *S. pneumoniae* and *S. agalactiae*, due to the low prevalence of CNS infection and the possibility of contamination [9,10]. Culture or additional PCR testing is necessary to confirm whether these test results are false positives. However, conducting these additional tests requires additional time and cost. While clinical symptom observation and other diagnostic tests can aid in differentiating between true and false positives, MPV along with CBC can provide rapid information without additional expenses. In our study, three patients had bacteria (*S. hominis*, *S. epidermidis*, and *S. capitis*) cultured from the CSF and one patient had *E. coli* detected by the FilmArray ME panel; however, they were considered to be contaminated by the attending physician. For these cases, the MPV values were 7.8, 8.1, 8.3, and 9.1, respectively, which were lower than the cutoff value of 9.7 determined in this study. Therefore, there is a possibility that MPV may serve as a useful marker, and further research in this area would be worthwhile.

This study has a few limitations. The number of patients admitted with infectious meningitis and had testing records was limited. Although 177 CSF cultures were positive, the majority of them (94%) were obtained from samples collected after neurosurgical procedures. The bacteria cultured in these cases could be attributed to postsurgical infections or contamination. Moreover, MPV in these patients might have been influenced by inflammatory responses following surgery or blood transfusion [11]. Therefore, those samples were excluded from the study to minimize confounding factors. Furthermore, excluding the patients with chronic inflammatory/hematological conditions or using anticoagulants/antiplatelet drugs did not sufficiently represent the disease groups. In future studies, it is necessary to investigate the distribution of MPV in groups of patients excluded from the study, as they may also be susceptible to infectious meningitis. Additionally, enrolling a larger number of patients would be beneficial for investigating the changes in MPV in bacterial meningitis across different clinical courses.

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**Declaration of Interest:**
No potential conflicts of interest relevant to this article were reported.

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