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Original Research Article

Evaluation of Neutrophil-to-Lymphocyte Ratio in Adult Bacterial Meningitis Cases in line with the Literature

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Abstract

The aim of this study was to assess neutrophil-to-lymphocyte ratio (NLR) as a prognostic factor in adult patients with bacterial meningitis. A retrospective, controlled and single center study was conducted between September 2013 and August 2019 after obtaining the required permission from Namik Kemal University, Research and Application Hospital Management. After the statistical calculation of the data obtained from the cases, the findings were systematically evaluated in the light of the literature. The results were found to be consistent with the literature. However, these results are from a retrospectively designed study carried out in a single center with a small sample group. Therefore, in order to crosscheck these results, it is urgent that they be confirmed through multi-centered and prospective studies with more cases involving each race and gender.

Keywords: Bacterial meningitis, Cerebrospinal fluid, Neutrophil-to-lymphocyte ratio, Procalcitonin

INTRODUCTION

Meningitis is the acute or chronic inflammatory diseases of the membranes surround the brain called meninges. The most common symptoms of the disease are fever, headache, confusion and stiff neck. Bacterial meningitis is a devastating infectious disease associated with increased mortality and loss of function despite advances in diagnostic and therapeutic methods. It can be seen in all age groups. As a result of the vaccinations against *Haemophilus influenza* type B, *Streptococcus pneumoniae* and *Neisseria meningitidis*, the incidence of bacterial meningitis has decreased, primarily childhood meningitis (Nau et al., 2013; Young and Thomas, 2018). The incidence in Western countries has gradually decreased to the ratio of 0.7-0.9 per 100.000 people, while in African countries it is approximately 25 times higher (Brouwer and van de Beek, 2018). The most important factor affecting treatment success in bacterial meningitis patients is immediate antibiotic administration.

In the presence of focal neurological deficit, papill edema, seizures or loss of consciousness, a computerized brain tomography scan is required. If there are no contraindications, cerebrospinal fluid (CSF) should be taken by lumbar puncture. Diagnosis can be made by using molecular tests on the fluid taken such as microbiological examination, biochemical analysis and polymerase chain reaction (PCR).

The differential diagnosis of acute bacterial meningitis threatening public health is very important both in terms of treatment choice and health economics. New, fast and easily calculated biomarkers are needed, especially in conditions of limited resources and in the presence of clinical examination findings.

Therefore, in this research, the aim of this study was to evaluate the prognostic relationship between neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker and meningitis.

MATERIALS and METHODS

During the review of the literature, eligibility criteria, double-blind, placebo-controlled, randomized clinical trials or level-I searches were included in our study (Kaplan, 2019; Karaarslan et al., 2019). A comprehensive and systematic literature search of numerous electronic databases (1905 Aug-2019 Sep), including the Cochrane Library, Ovid, the National Library of Medicine at the National Institutes of Health was performed.

Data were obtained retrospectively from patient archive files and hospital automation system. Data were compiled and listed in an Excel file. Then, the data were evaluated statistically.

Statistical Analyses

Data obtained from the cases were assessed through Minitab version 18.0. Descriptive statistics were presented as mean ± standard deviation or frequency (%). The NLR was defined as follows: NLR=N/L, where N and L were the neutrophil and lymphocyte counts before treatment, respectively (Pan et al., 2019).

Mann-Whitney U test was used to compare the two groups because the data did not comply with the parametric test assumptions. For multivariate analyses, since the diagnosis of bacterial meningitis was considered a dependent variable, the independent variables that could affect the dependent variable and OR were analysed using logistic regression analysis. The validity of a parameter was analysed using ROC. Likelihood ratio (LR +), sensitivity and specificity were calculated. LR + = Sensitivity / (1-Specificity). Two-tailed P values of less than 0.05 were accepted to be statistically significant (Bilir et al., 2015).

RESULTS

Of the cases who met the research criteria, 27.27% (n=11) were female, and the mean age of all the cases was 45.45±20.99 years. No significant difference was observed between groups in terms of mean age (*P*= 0.875).

It was understood from the archive files that routine 8-15 ml fluid was taken with 20-22 gauge spinal needles by lumbar puncture and transferred to four sterile tubes. These samples taken and transferred to four different tubes were understood to have been labelled according to the order of taking as tube 1 tube to be used for biochemistry and serology, tube 2 for microbiological analysis, and tube 3 for cell counting, while tube 4 was reserved for microbiological and additional serological tests.

In the file data, no record was found regarding any complications such as herniation, spinal hematoma and cord compression, iatrogenic infection, headache and/or back pain in any of the cases from whom sample fluid was taken by lumbar puncture.

As a result of the evaluation of the laboratory data of blood and CSF, it was found that the mean CSF protein amount was 221.81±87.66-g/dL, the mean CSF glucose amount was 28.81±23.71-g/dL, but the CSF glucose amount decreased in all cases except three cases. It was remarkable that the mean of platelet values was 263.37±130.13 -10.^{3}/µl-. In addition, in these patients diagnosed with bacterial meningitis, laboratory findings with extremely high values were found (Table 1).

Table 1. The CSF and peripheral vein parameters.

Parameters	Mean±SD
CRP (mg/L)	232.46±118.4
ESR (nm/hour)	62±27.17
CCC (cell counting/mm^3)	2540±3116.62
WBC (10^3/µl)	18:41±7.86
PCT (ng/ml)	5.5±7.69
N (10)^3/µl)	17.4±0.75
L (10^3/µl)	6.46±2.76
N/L (NLR)	2.69±0.28

SD stands for Standard deviation, CRP for C-Reactive protein, ESR for Erythrocyte Sedimentation Rate, CCC for number of cells in CSF, WBC for Leukocyte, PCT for Procalcitonin, N for Neutrophilia, L for Lymphocyte, and N/L=NLR refers to Neutrophil Lymphocyte Ratio.

Comparison of peripheral vein parameters between cases. Logistic regression analysis, which was used to monitor the changes in hemogram parameters, showed N/L odds ratio (OR) as 5.66 (p=0.005, 95%CI: 1.479-10.613). OR values of ESH, PCT and CRP were found to be 1.897 (p=0.031, 95%CI: 1.012- 3.857); 1.247 (p=0.023, 95%CI: 1.011- 2.857), and 1.06 (p<0.05, 95%CI: 1.014- 1.124), respectively. The NLR curve of the bacterial meningitis patients was observed to be over the reference line, and the area under the line was 0.798 (*P*<0.05; 95% CI, 0.987–0.999), which is very close to 1. In the NLR validity calculation, the highest LR positive value was 10.75 and NLR was found to be 2.69. At this point, when the cutoff point for NLR was taken as 2.69, our method was observed to have a sensitivity and specificity of 86% and 91%, respectively.

Brucella and/or anti-HIV results were observed to be negative in the cases. It was seen that no agent was detected in the results of polymerase chain reaction (PCR) performed for screening CSF TBC, Cytomegalovirus and/or Herpes Simplex virus and human herpes virus.

It was reported that culture and PCR results were consistent in three cases, while only culture was performed in the remaining cases, and no PCR test was reported to be carried out. It was seen that the agent which was isolated the most was *Streptococcus*

pneumonia.

It was understood that in the antibiotic therapy, ceftriaxone, ceftriaxone, vancomycin, ceftazidime, meropenem or ampicillin sulbactam were administered. After antibiotic therapy, it was understood that infection markers returned to normal values, a sequela was observed in one female patient, and all other cases recovered and were discharged.

DISCUSSION

For the first time in the literature, in addition to adult cases, a study was conducted in 1989 for the diagnostic value of haematological parameters in cases diagnosed with meningitis. In that study, infants under the age of four (n=72) diagnosed with meningitis were included in the study. After the statistical evaluation of the data obtained, the researchers inferred that the CBC differential ratio being less than 1.5 could accurately predict all neonatal bacterial meningitis cases with 99.95% confidence. In addition, the researchers of the study interpreted that the use of this parameter (CBS differential ratio) in conjunction with other conventional tests was effective in predicting the outcome.

During clinical practice, low CSF glucose value and increase in neutrophil and leukocyte are accepted as indicators of bacterial meningitis. The PCT value is also a parameter gaining popularity, as it may yield results earlier than WBC count and blood culture tests. As it is known, the PCT value is a parameter which can indicate the presence of bacterial infections and can be used in the detection of bacterial infections, and serum levels should be below 0.1 ng/ml in healthy adults. The CSF glucose concentration is lower than plasma but ranges between 45-80 mg/dl. CSF glucose value is known to display variations in suppurative meningitis, tuberculous meningitis, leukemic meningitis, leptomeningeal cyst and hypoglycaemia. In addition to all these, it is also known in the literature that the most frequently examined test in CSF is protein measurement and its normal level should be between 15-45 mg/dl.

In their study, Kim et al. (2017) divided the cases in two groups in terms of the presence of pleocytosis and examination of CSF samples with the suspicion of central nervous system infection. They reported that in cases without pleocytosis (n=56), the NLR value was9.1 (5.1–13.3), and the CRP value was found to be 21.0 (9.0 - 61.0). They also reported that this NLR value was found to be NLR 4.4 (3.0–7.3) and CRP level was 5.0 mg/L (5.0–9.0) in patients with pleocytosis (n=45). Based on these findings, they concluded that when NLR≥6 and CRP ≥12.7 mg/L is the case, the focus of infection should be sought outside the central nervous system (Kim et al., 2017).

However, this result they reached is not in line with the results obtained from this study. This is because it is a widely accepted fact that the increase in the cell number in CSF above 10 at mm^3 is considered to be pathological and that increase in the number of cells in CSF samples is a marker of meningeal irritation. In this study, it was determined that the number of cells in CSF samples of the cases increased and reached 2540 level at mm^3, which could be identified as pleocytosis. And it is seen that there is a positive correlation between high NLR ratio and pleocytosis in these cases.

Moreover, the findings obtained from this study are inconsistent with the literature except for the study of Kim et al. (2017). The results obtained from this study are consistent with the results of various studies in which NLR was described as a diagnostic and prognostic parameter in patients with sepsis. (Kauishik et al., 2018), where NLR had no effect on mortality but was associated with clinical outcomes (Salciccioli et al., 2015), and many other studies with high evidence of value (Brouwer and van de Beek, 2019; Chen et al., 2019; Mentis et al., 2017) , and in the diagnosis of bacterial meningitis, a positive correlation between NLR increase and prognosis of the disease was shown.

In the study in which the clinical and microbiological features of HIV-associated tuberculous meningitis were evaluated in Vietnamese adults, 58 cases were included for evaluation. Among the findings they reported after the evaluation of CSF samples, the median cell count was 438/mm^3 (63% N%), 69% Ehrlich-Ziehl-Neelsen (EZN) was staining positive and 87.9% was culture positive (Torok et al., 2008).

Sumanth et al. (2018), in their study, aimed to determine optimal CSF lactate cut-off values in their populations in order to evaluate the prognostic effect of CSF lactate in postoperative bacterial meningitis (POBM). In that prospectively designed study based on data from 2012 to 2014, in which they included all the patients (n=37) who had undergone intradural cranial surgery with their postoperative bacterial meningitis characteristics, they reported that N, L and WBC values were prognostic (Sumanth et al., 2018).

They also underlined that improvement in CSF/blood glucose ratio and decrease in CSF cell number correlated with each other. It has been reported that CSF lactate level has a reliable prognostic value in POBM, and that the effect of routine CSF markers is not clear. They, therefore, concluded that CSF lactate value could be considered as a better alternative for both diagnosis and prognosis (Sumanth et al., 2018).

In this study, although CSF lactate values were not available in the files of the cases, it was understood from the laboratory parameters obtained from the cases with bacterial meningitis that NLR and PTC increase was in correlation with the prognosis of bacterial meningitis.

Tuberculous meningitis is one of the central nervous system infections with the highest mortality and sequelae, but few reports describe long-term clinical outcomes and prognostic factors. Accordingly, the clinical features of

adult tuberculosis meningitis cases (n=154) in China with a mean age of 41 years were examined retrospectively between 2012 - 2015. In these cases, they reported the presence of high levels of NLR. As a result, they interpreted that NLR might be a prognostic factor in patients with tuberculous meningitis (Li et al., 2017).

Chen et al., in their study in which they examined the relationship between the sensitivity and group characteristics of group B Streptococcus (GBS) that caused meningitis in Chinese infants and mannose-binding lectin (MBL) deficiency (Chen et al., 2019), evaluated the data belonging to 33 infants diagnosed with laboratory-approved GBS meningitis. They reported that in comparison to the control group, significantly higher MBL variant genotype A/B was detected in infants who were ill, and high NLR values and high C-reactive protein were observed (Chen et al., 2019).

In this study, adult cases were evaluated, rather than infant cases. It is understood that in laboratory tests of adult cases, the MBL variant and/or any other variant were not investigated.

In a similar study (Mentis et al., 2017), NLR in CSF content has been reported to be useful in distinguishing bacterial and viral meningitis. Considering that meningitis is clinically heterogeneous in terms of age, they investigated the validity of CSF-NLR and neutrophil test in 4.000 meningitis cases between 2006 and 2013 by age group. They reported that the distribution of bacterial and viral meningitis was heterogeneous between age groups with a low rate of bacterial meningitis in cases aged 5-14 years. They also reported that CSF-N number and NLR values were significantly more discriminatory in patients over the age of 14 than those in the 0-14 age group in terms of bacterial meningitis. Based on these data, they concluded that age-related N and NLR may help improve diagnostic tests of meningitis in meningitis cases (Mentis et al., 2017).

To conclude, in this study, it was determined that the number of cells in CSF samples taken from patients diagnosed with bacterial meningitis increased to the level of 2540 (pleocytosis) at mm^3. And, the mean CSF glucose value was determined as 28.81±23.71-g/dL. In addition, the amount of CSF protein was observed to be 221.81±87.66-g/dL. As important as all these findings, it was determined that the PCT value of these cases was 5.5±7.69 ng/ml, and that NLR statistically significantly increased ($P<0.05$).

CONCLUSION

The results of this research should be verified through the results of world-wide, multi-centered researches with the participation of volunteers of all genders and races. Only in this way, it would be possible to obtain invaluable information on the differential diagnosis and treatment choice of acute bacterial meningitis. PCT and NLR levels may contribute to diagnosis, especially in conditions of limited resources and in the presence of clinical examination findings.

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