Higher Neutrophil-To-Lymphocyte Ratio is Associated with Depressive Symptoms in Japanese General Male Population

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Abstract

Relationships between the neutrophil-lymphocyte ratio (NLR) and/or the platelet-lymphocyte ratio (PLR) and neuroinflammatory diseases have been reported. Depression is also associated with neuroinflammation. Here, we determined the association between the NLR, PLR, and depression. This cross-sectional study is a secondary analysis of the data of the Iwaki Health Promotion Project 2017. We analyzed the characteristics and laboratory data of 1,015 Japanese subjects (597 females, 408 males) including their NLR and PLR values. We assigned the subjects with a Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 to the depression group. We performed a multivariate logistic regression analysis to determine whether the NLR and/or PLR were associated with depressive symptoms (CES-D ≥ 16). Two hundred subjects (19.7%; 122 [20.4%] females, 78 [19.1%] males) were assigned to the depression group. There were significant differences between the depression and non-depression groups in the NLR [median (25th to 75th percentile): 1.54 (1.24, 1.97) vs. 1.76 (1.32, 2.37), $p=0.005$] and the PLR [median (25th to 75th percentile): 123.7 (102.0, 153.9) vs. 136.8 (107.0, 166.5), $p=0.047$] in males, but not in females. The multivariate logistic regression analysis demonstrated that the NLR was significantly associated with depression in the males (adjusted odds ratio: per 1 increase, 1.570; 95% confidence interval: 1.120–2.220; $p=0.009$). In conclusion, our findings indicate that higher NLR may be associated with depressive symptoms in males.

Introduction

Although the mechanism and pathogenesis of the development of depression are not yet clear, neuroinflammation is known to play an important role in depression ^[1,2]. The blood concentrations of inflammatory cytokines such as interleukin 6 and tumor necrosis factor- α were reported to increase in patients with depression ^[3,4].

The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), which are calculated as the neutrophil and platelet counts respectively divided by the lymphocyte count, are convenient and inexpensive inflammatory markers. The NLR was reported to be associated with the development of neuroinflammatory diseases such as delirium and cognitive dysfunction ^[5,6]. Several studies demonstrated that the NLR was significantly increased in patients with depression ^[7–10], and a study demonstrated that the PLR was significantly increased in patients with severe depression plus psychotic features compared to patients with mild-to-severe depression ^[11]. However, four of these five studies had small sample sizes ^[7–9,11], and the other study ^[10] focused on only patients with diabetes mellitus (DM). Thus, the utility of the NLR and the PLR for the screening of patients with depression has not been elucidated.

The present study was conducted to determine the associations between the NLR and the PLR and depression using relatively 'big data' of Japanese community dwellers.

Methods

Study design and subjects

This population based cross-sectional study is a secondary analysis of the data of the Iwaki Health Promotion Project 2017 which was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine (2017-026). Iwaki Health Promotion Project was registered with the University Hospital Medical Information Network (UMIN 000040459, April 1, 2014) and this study was conducted in accordance with the recommendations of the Declaration of Helsinki. All participants in this project gave written informed consent for the publication of their data. We herein analyzed the data of the 1,073 Japanese volunteers who live in the Iwaki district of the city of Hirosaki, Japan. Participants with a clinical diagnosis of depression (n=6) or missing data (n=52) were excluded from the present analyses, leaving a final total of 1,015 subjects.

Data collection

Demographic data and medical information were obtained from self-reported questionnaires. Blood samples were obtained in the early morning from the medial cubital vein of the subject in a sitting position after he or she had fasted overnight. The following collected blood data were used: peripheral blood cells, aspartate transferase (AST), alanine transferase (ALT), blood urea nitrogen (BUN), creatinine (Cre), hemoglobin A1c (HbA1c), and B-type natriuretic peptide (BNP).

Each subject's NLR and PLR were determined as the absolute neutrophil or platelet count divided by the absolute lymphocyte count, respectively.

Assessment of depressive symptoms

We used the Center for Epidemiologic Studies Depression Scale (CES-D) to assess the prevalence and severity of depressive symptoms in the subject population. This scale is a short self-report scale designed to measure depressive symptomatology in the general population. The maximum score is 60, and higher scores are associated with greater depression. Because the reported optimal cutoff CES-D score for the assessment of depression in a general population is ≥ 16 ^[12], we assigned the subjects with CES-D scores ≥ 16 and ≤ 15 to the depression and non-depression groups, respectively.

Statistical analyses

Each analysis was performed separately for the males and females, because sex differences in both the NLR and PLR have been reported ^[13]. All data are presented as the median (25th and 75th percentiles), the number (a percentage of each group), or adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs). Differences in continuous variables between two groups were assessed using the Mann-Whitney test, and differences in categorical variables were assessed using Fisher's exact test.

Multivariate logistic regression analyses were performed to examine whether the NLR and/or PLR are associated with depressive symptoms after adjusting for possible confounding factors. The subjects' NLR and PLR values were forced into the model as explanatory variables. As age and body mass index

(BMI) were reported to be associated with both the NLR and PLR ^[13,14], they were also included to the model. As comorbidities, hypertension, DM, dyslipidemia, coronary artery disease (CAD), and stroke were reported to be associated with depression ^[15–17], and we thus included these in the model. In addition, the variables with p-values <0.2 in univariate analyses were included in the multivariate model not to miss confounders. The variance inflation factor (VIF) was used to check for multicollinearity in each variable. Discrimination was measured by using the area under the curve (AUC). The fitness of the model was evaluated with using Hosmer-Lemeshow test.

All data analyses were performed with EZR software ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P-values<0.05 were considered significant in all tests.

Results

The subjects' characteristics

We analyzed the cases of the 1,015 subjects (597 females [59%] and 408 males [41%]) (Fig. 1). The prevalence of depression (CES-D score ≥ 16) was 19.7%; we assigned these 200 subjects with depression (122 [20.4%] females, 78 [19.1%] males) to the depression group.

The subjects' characteristics are summarized in Table 1. There was no significant difference between the depression and non-depression groups in the subjects' characteristics except for the rate of alcohol drinker in the males. The multivariate logistic regression analysis showed that alcohol drinker was significantly associated with depressive symptoms in the males [aOR:0.548; 95% CI: 0.322–0.930; p=0.026)] (Table 3).

The NLR, the PLR, and depression

There were significant differences between two groups in the NLR [median (25th to 75th percentile): 1.54 (1.24, 1.97) vs. 1.76 (1.32, 2.37), p=0.005] and the PLR [median (25th to 75th percentile): 123.7 (102.0, 153.9) vs. 136.8 (107.0, 166.5), p=0.047] in males, but not in females (Table 2). The multivariate logistic regression analysis demonstrated that the NLR was significantly associated with depressive symptoms in the males (aOR: per 1 increase, 1.570; 95% confidence interval: 1.120–2.220; p=0.009) (Table 3).

Discussion

We examined the cross-sectional association between the NLR and the PLR and depression in a general population. The results of our analyses demonstrated that after the adjustment for possible confounding factors, a higher NLR was significantly associated with depressive symptoms in males. In addition, alcohol drinker was significantly associated with a lower risk of depressive symptoms in males.

Neuroinflammation caused by a chronic activation of microglia (which produce excessive levels of inflammatory cytokines) is involved in the mechanism of depression ^[18]. Both the NLR and the PLR are

known to be possible inflammatory markers [5, 6]. In the present study, although the univariate analysis indicated that both the NLR and the PLR were significantly higher in the depression group than in the non-depression group, the multivariate analysis revealed that only a higher NLR was associated with the development of depressive symptoms in only the males after adjusting for possible confounders. In contrast, Kayhan et al. reported that the PLR was significantly increased according to the severity of depression; the difference between our findings and their data may be due to the study population [11]. This study did not include healthy controls, whereas our study included healthy subjects without clinically diagnosed depression.

The lifespans of neutrophils and platelets in human are <24 hr [19] and >10 days [20], respectively. The NLR and the PLR may thus reflect acute and chronic inflammation, respectively. As patients with a clinical diagnosis of depression may have chronic neuroinflammation, the PLR could be a better reference to assess the severity of depression. The NLR may be suitable for assessing subjects with a lesser degree of depressive symptoms who are not diagnosed as having depression. The NLR may also promptly reflect the effects of treatment, as an earlier study showed that the improvement in depressive symptoms provided by treatment with selective serotonin inhibitors was accompanied by a reduction in the patients' NLR [8].

To the best of our knowledge, the present study is the first to demonstrate the association between a higher NLR and depressive symptoms in males but not in females. Although the mechanisms underlying sex-related differences in the NLR remain unclear, the estrogen level may be attributed to the difference [21,22]. Wu et al. reported that the NLR at the ages of 30–49 years was higher in females than in males, while the NLR at the ages of 60–69 was higher in males than in females [23]. This may be due to postmenopausal estrogen depletion. Indeed, we observed a significant but weak negative correlation between age and the NLR in females ($B = -0.005$, $R^2 = 0.007$, $p=0.037$). A large cohort study is needed to determine whether the NLR can be used as a potential reference for the development of depression.

We also observed that alcohol drinker was significantly associated with a lower risk of depressive symptoms in males. Similarly, Gémes et al. reported that light-to-moderate alcohol consumption was associated with the lowest risk of depression [24].

There are some limitations of our study. First, as this was a retrospective cross-sectional study, we cannot provide definite information about cause-and-effect relationships and changes in the NLR and depressive symptoms over time. Additionally, there might be undetected confounding factors that affected the results. Second, as this study was limited to Japanese subjects living in a specific area, possible racial and regional differences were not considered. Third, as we did not include patients with a clinical diagnosis of depression, our results might not be applicable to all patients with depression. On the other hand, this result suggests the potential of the NLR for screening depressive symptoms in general populations, as a strength of this study.

In conclusion, this population based cross-sectional study demonstrated that a higher NLR was significantly associated with depressive symptoms in males but not in females. Prospective longitudinal studies are required to confirm the relationships between the NLR and depression.

Declarations

Data availability

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

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Author contributions

All authors evaluated data and reviewed the manuscript. H.K. designed the study and drafted the manuscript. D.T performed the statistical analysis, and prepared figure and tables 1-3. K.S. collected data. K.H. extensively revised the manuscript.

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Competing Interests

All authors declare no competing interests.

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Tables

Due to technical limitations, table 1,2,3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Study population flowchart.

Supplementary Files

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- [Table1.jpg](#)
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