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ORIGINAL ARTICLE

Association between neutrophil-to-lymphocyte ratio and length of hospital stay in an acute psychiatric hospital: A cross-sectional study

Rikako Tsuji MD, MPH [ORCID] | Yuto Hiura MD | Yuki Ishikura MD, MPH | Toshinari Sueyoshi MD | Naoaki Sho MD, PhD | Naoki Narushima MD, PhD | Takeshi Haoka MD, PhD | Atsushi Terao MD | Akira Kikuchi MD, PhD

Urawa Neuropsychiatric Sanatorium, Saitama, Saitama, Japan

Correspondence
Rikako Tsuji, MD, MPH, Urawa Neuropsychiatric Sanatorium 301-1, Hirogayako, Minami-ku, Saitama 336-0041, Japan.
Email: tsujirik@gmail.com

Abstract

Aim: The available evidence for predicting length of stay in acute psychiatric hospitals includes demographics, diagnosis, and treatment variables. This study aimed to evaluate the association between neutrophil-to-lymphocyte ratio (NLR) and length of hospital stay in an acute psychiatric hospital.

Methods: A total of 116 patients who were admitted to an acute psychiatric ward at Urawa Neuropsychiatric Sanatorium (Saitama, Japan) from August 2022 to December 2022 were eligible for this study. Laboratory data of lymphocytes and neutrophils were assessed on the first day of admission and NLR was calculated based on the data. Participants were categorized into two groups, high NLR and low NLR, which were set as predictor variables, as well as using NLR as a continuous variable. Multiple linear regression was performed to determine the association between NLR and length of hospital stay, adjusting for confounding factors.

Results: A total of 90 participants were included in this study. The association of NLR as a continuous variable and length of hospital stay was not significant. When we categorized participants into high- and low-NLR groups, the association was significant even after adjusting by covariates ($p < 0.05$).

Conclusion: Categorized NLR was positively associated with the length of hospital stay in patients admitted to an acute psychiatric hospital. Categorized NLR may predict the length of hospital stay for patients who are admitted to an acute psychiatric hospital.

KEYWORDS
inflammation, length of hospital stay, neutrophil-to-lymphocyte ratio (NLR), psychiatric disorder

INTRODUCTION

Length of hospital stay has been an important indicator in acute psychiatric hospitals. The available evidence for predicting length of stay in acute psychiatric hospitals includes demographics such as gender or age, diagnosis, and treatment variables.[1] In addition, multiple factors related to characteristics of patients, the hospital, and psychiatrists providing care are likely to interact to determine the length of hospital stay.[2] These studies mainly focused on social factors or subjective assessment. To the best of our knowledge, there is

no research that emphasizes the use of objective parameters to predict the length of hospital stay.

Neutrophil-to-lymphocyte ratio (NLR) has been widely used as an accessible marker of systemic inflammation in various diseases, including tumors and infection, as it is associated with an increase in cytokines and C-reactive protein.[3] Neutrophils act as a rapid response to infection and stand for non-specific inflammation.[4] On the other hand, lymphocytes reflect specific immunity and play an important role in adaptive immunity.[5] Since it indicates the ratio of two opposite but complementary immune pathways, it is noteworthy that compared to white blood cell, NLR is suitable for detecting overall inflammation, which is less influenced by physiological conditions.[6]

Recent studies have also proposed that NLR may be useful as an inflammatory biomarker in psychiatric patients[7] because monocytes, neutrophils, T cells, and B cells cross the blood–brain barrier and may contribute to disease progression.[8] In fact, NLR was found to be elevated in a portion of adult patients with schizophrenia,[9–14] major depressive disorder,[15] and bipolar disorder.[16] In addition, NLR is related with psychiatric symptoms regardless of the type of disease, and increased levels of NLR are significantly associated with the existence of first-episode psychosis.[17,18] Since NLR is inexpensive and easy to calculate from the complete blood count by dividing the number of neutrophils by the number of lymphocytes, it may be useful in clinical practice to estimate the risk and length of hospitalization in psychiatric patients.

However, to date, there is no evidence that suggests the usefulness of a biomarker in predicting the length of hospital stay in psychiatric patients, although one study revealed that NLR could also be a predictor of in-hospital mortality in the geriatric population.[19] To overcome this deficit, the current study examines the association between NLR and length of hospital stay in an acute psychiatric hospital. We hypothesized that the length of hospital stay would be positively associated with NLR on admission. The purpose of our study is to determine whether NLR could provide information that can be effective as a biomarker in predicting the length of hospital stay at a psychiatric hospital.

METHODS

Sample

The current study employed a descriptive cross-sectional design. Participants admitted to an acute psychiatric ward at Urawa Neuropsychiatric Sanatorium (Saitama, Japan) from August 2022 to December 2022 were eligible for this study. This hospital is a psychiatric hospital with 263 beds located in the southern part of Saitama City in Saitama Prefecture. Currently, 48 beds are for patients with emergency status, which proposes that 60% of patients would be expected to be discharged within 3 months. Patients were excluded from the study if they met one or more of the following criteria: transfer from a different ward within the hospital, transfer from a different hospital because of a physical problem, transfer to a different hospital because of a physical problem, and refusal of the patient to participate in the study. The original protocol planned to follow the patient for 1 year after admission. Patients who were still hospitalized at the end of the study were excluded from the analysis. Clinically significant abnormalities on the baseline physical examination, such as fever or tachypnea, were also criteria for exclusion from study participation. Patients were diagnosed according to the *International Classification of Diseases-10* (ICD-10; World Health Organization[20]). After admission, the patients were treated by trained psychiatrists. Informed consent was obtained from all participants or from parents/legal guardians in subjects under 18 years prior to entering this study on the first day of admission. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The local ethics committee of Urawa Neuropsychiatric Sanatorium approved the study (No. 2022001). The participant recruitment flowchart is shown in Figure 1.

Study assessment

At baseline, a complete medical history was taken. Laboratory data of lymphocytes and neutrophils were assessed on the first day of admission. For the measurement of complete blood count, blood was drawn into a vacutainer tube containing EDTA as an anticoagulant tube and sent to the defined site laboratory for analysis. On the first day of admission, we also assessed psychiatric symptoms using the Brief Psychiatric Rating Scale (BPRS).[21]
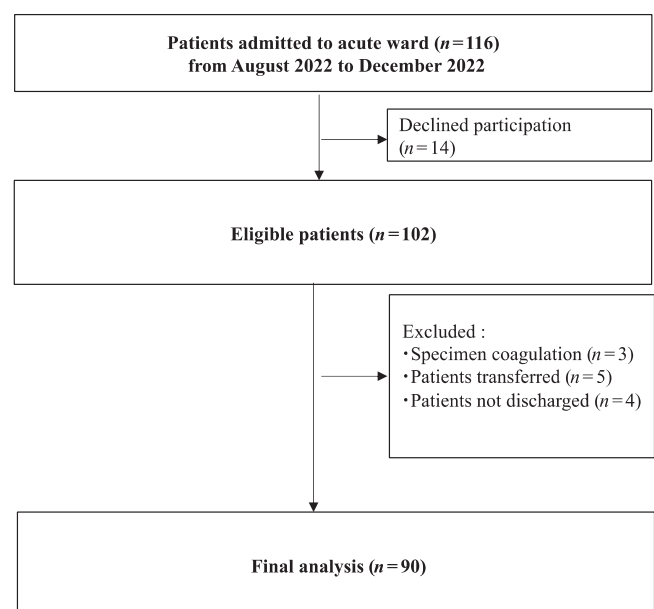

FIGURE 1 Flowchart of the participants.

Statistical analysis

Statistical analyses were conducted using R Version 4.0.3. Multivariate analysis was used to test whether gender and age could affect NLR. A significance level of 0.05 was considered statistically significant. NLR was used as a predictor variable. First, we used NLR as a continuous variable. Second, participants were categorized into two groups: those with high NLR (above 1.65) and those with low NLR (below 1.65), based on the mean NLR of the health population. To date, there is no approved cut-off NLR value that discriminates normal from abnormal values. Previously there were only three studies stating the NLR in the general population. The normal average was 1.65 in the Belgian study[22] and the Korean study.[23] One study pointed out that the normal value of NLR differs from ethnicity and gender.[24] As our sample was from an Asian population, we set the cut-off score for 1.65. The length of hospital stay was the outcome variable. We used a multivariate linear regression model to see the association between NLR and length of hospital stay. We fitted three models. Model 1 evaluated crude association without adjusting for covariates, and Model 2 adjusted for age and gender. Model 3 additionally adjusted for BPRS. For sensitivity analysis, we employed the same statistical method, including those who were still hospitalized.

RESULTS

Figure 1 shows the flowchart of the participants. A total of 116 potential participants were admitted to an acute ward from August 2022 to December 2022. Of the patients admitted, 14 declined participation, five were transferred to different hospitals, three with specimen coagulation were excluded from the analysis, and four patients were still hospitalized 1 year after admission. After excluding these patients, 90 were included in the final analytic sample. Table 1 shows the demographic characteristics of the sample. The gender of the participants was almost equal, and the average age was 51 years, ranging from 17 to 91 years. Most patients were diagnosed as a category of F2 (54%) or F3 (18%). In the low-NLR group, the mean average of hospital stay was 44.9 days, whereas in the high-NLR group the stay was longer, with a mean average of 73.4 days. Tables 2 and 3 present the results of the multiple linear regression. The association between NLR as a continuous variable and length of hospital stay was not significant (Table 2). On the other hand, NLR as a categorical variable and length of hospital stay was significantly associated ($p < 0.05$). Adjusting covariates did not attenuate the association (Table 3). We additionally conducted a sensitivity analysis by including those who were still hospitalized at the end of the protocol. In Supplementary Materials 1-1 and 1-2, the length of hospital stay of these patients was set as 1 year based on the original protocol. In Supplementary Materials 1-3 and 1-4, their length of hospital stay was calculated from the day of their admission to June 30, 2024, when our last analysis was performed. Similar to our results, NLR as a categorical variable was significantly associated with

length of hospital stay ($p < 0.05$), whereas NLR as a continuous variable was not significantly associated with length of hospital stay.

TABLE 1 Demographic characteristics of the participants.

	N (%)	Average (SD) Median (Min, Max)
Age (years)		51.2 (19.8)
		52.0 (17.0, 91.0)
10–19	5 (5.6)	
20–29	10 (11.1)	
30–39	15 (16.7)	
40–49	13 (14.4)	
50–69	24 (26.7)	
70≤	23 (25.6)	
Gender		
Men	43 (47.8)	
Women	47 (52.2)	
ICD		
F0	7 (7.8)	
F1	2 (2.2)	
F2	49 (54.4)	
F3	16 (17.8)	
F4	6 (6.7)	
F5	0 (0)	
F6	1 (1.1)	
F7	7 (7.8)	
F8	2 (2.2)	
Length of hospital stay		
<2 weeks	9 (10.0)	
<1 month	12 (13.3)	
<2 months	27 (30.0)	
<3 months	25 (27.8)	
>3 months	17 (18.9)	

Abbreviation: ICD-10, International Classification of Diseases-10.

DISCUSSION

From our study, we found that patients with high NLR as a categorical variable were associated with longer hospital stays compared to patients with low NLR on admission. This result may be in line with previous studies showing that high NLR was associated with psychiatric diseases or symptoms. A variety of mechanisms involving the immune system and the inflammatory pathophysiology of psychiatric

TABLE 2 Association between NLR as a continuous variable and length of hospital stay.

	N (%)	Estimate	Standard error	T	p-value
Overall	90 (100)				
Model 1		3.09	3.23	0.96	0.341
Model 2		2.66	2.91	0.91	0.364
Model 3		3.03	2.91	1.04	0.302

Note: Multiple linear regression was performed. NLR was a predictor variable, and length of hospital stay was the outcome variable. Model 1 evaluated crude association without adjusting for covariates, and Model 2 adjusted for age and gender. Model 3 additionally adjusted for BPRS.
Abbreviations: BPRS, Brief Psychiatric Rating Scale; NLR, neutrophil-to-lymphocyte ratio.

TABLE 3 Association between categorized NLR and length of hospital stay.

	N (%)	Estimate	Standard error	T	p-value
Overall	90 (100)				
Model 1		28.5	11.7	2.42	0.017
Model 2		24.0	10.6	2.26	0.026
Model 3		26.5	10.6	2.49	0.015

Note: Multiple linear regression was performed. NLR was categorized into high- and low-NLR groups as a predictor variable, and length of hospital stay was the outcome variable. Model 1 evaluated crude association without adjusting for covariates, Model 2 adjusted for age and gender. Model 3 additionally adjusted for BPRS.
Abbreviations: BPRS, Brief Psychiatric Rating Scale; NLR, neutrophil-to-lymphocyte ratio.

diseases are reported, and high NLR is related to the existence of psychiatric disease or psychosis. For patients with high NLR and psychiatric symptoms, the duration of hospitalization might be longer. Assessing NLR at admission is important, since the gap between the high-NLR group and the low-NLR group was smaller after 1 month post admission (Supplementary Material 2). This result is similar with the study that showed that NLR was associated with first-episode psychosis, implying that patients with first-episode psychosis present an increased mean NLR at the very beginning of the disorder.[17] From our research, the mechanism of why a higher value of NLR was significantly associated with longer hospital stays remains uncertain. The underlying pathophysiology of the significant correlation between psychiatric diseases and inflammation is still controversial, which adds another layer of complexity. One study pointed out that the effective use of augmentation with anti-inflammatory agents may have a dual and possibly synergistic effect: by decreasing the inflammation that generates the disorder and also by directly improving the symptoms.[25] From this point of view, high NLR could reflect the longer time required to alleviate the inflammation. Furthermore, high and low NLR levels may have different effects on the medication. Thus, the drug sensitivity of these two

groups should be examined in our future studies. From our study, no differences were observed in the scores of BPRS between the high-NLR and low-NLR groups, and the linkage between inflammation and the exhibited symptoms is still unclear (Supplementary Material 3). However, the significant association between categorical NLR and length of hospital stay even after adjusting for BPRS may imply that categorical NLR could be one of the indicators to predict the length of hospital stay. Though BPRS is also based on the psychiatrist's subjective evaluation and confirming the psychiatric symptoms in another appropriate assessment measure may be an additional challenge, the possibility of using biomarkers of inflammation for the categorical diagnosis or treatment evaluation apart from subjective assessment might be one of the future expectations.

Nevertheless, the raw data of NLR and length of hospital stay were not significantly associated, which was different from our hypothesis. Since our data of NLR exhibit non-normal distribution, including some cases of outlier values (Supplementary Material 4), our result may have been distorted, contributing to inconsistency with the result using NLR as a categorical variable. We need further confirmation with a larger number of patients to guarantee precise analysis.

The strength of our study is that it is the first to examine the association between one of the biomarkers of inflammation in patients with psychiatric symptoms and length of hospital stay. NLR is an inexpensive and easy biomarker to check in routine laboratory testing, and it may be useful in determining the prognosis of patients. Detecting the possibility of a longer hospital stay on admission based on NLR may lead to early intervention on admission. For example, we may consider the use of anti-inflammatory pharmacological treatment for high-NLR patients.[25] Psychosocial intervention could be another option since major life stressors, especially those involving interpersonal stress and social rejection, affect the immune system in psychiatric disorders.[26] In the future, we may also need to conduct a longitudinal study to find out whether the type of disease or treatment is linked to changes of NLR and confirm the objective elements to avoid extended length of hospital stay.

LIMITATIONS

Our study has several limitations. First, residual confounding factors, including drug treatment, tobacco use, BMI, or the number of admissions, were not assessed in this study. Particularly, the discharge destination may also affect the analysis. Since four patients were still hospitalized and the length of hospital stay was unknown, we could not include them in the analysis. However, these patients were also in the high-NLR group. The reasons for continuous hospitalization include the obstacles of family conflict and waiting for the availability of a patient's preferred discharge placement. Social factors, including the adjustment of discharge, should also be taken into account. Second, the nature of a cross-sectional study does not explain causal relationships. Length of hospital stay is related with a variety of factors, such as the treatment or type of disease, and the

mechanism of association between NLR and length of hospital stay is still unclear. Assessing other potential inflammatory biomarkers, including C-reactive protein,[17] monocyte-to-lymphocyte, and platelet-to-lymphocyte ratio,[27,28] which are reported to be associated with psychiatric disorders, may be helpful in confirming the mechanism of our result. Third, since our finding is from a single psychiatric institution, our result may not be generalized to all populations in Japan. Future study is needed with larger samples of populations with psychiatric symptoms. Fourth, the cut-off score of NLR was based on limited studies from the general population which may influence our analysis. Moreover, the analysis using raw data of NLR was not significant, which needs to be confirmed in a larger sample size in future study.

CONCLUSION

We can conclude that categorized NLR was positively associated with the length of hospital stay in patients admitted to an acute psychiatric hospital. Categorized NLR may predict the length of hospital stay in patients admitted to an acute psychiatric hospital.

AUTHOR CONTRIBUTIONS

Conception and design: Rikako Tsuji and Akira Kikuchi. *Acquisition of data*: Rikako Tsuji, Yuki Ishikura, Yuto Hiura, Toshinari Sueyoshi, and Akira Kikuchi. *Interpretation and data*: Rikako Tsuji. Akira Kikuchi, Takeshi Haoka, Atsushi Terao, Naoaki Sho, and Naoki Narushima ensured that the study was appropriately investigated and resolved. Rikako Tsuji participated in writing the manuscript. All authors have critically read and approved the manuscript. The manuscript has not been previously published nor is it being considered for publication elsewhere.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

ETHICS APPROVAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The local ethics committee of Urawa Neuropsychiatric Sanatorium approved the study (No. 2022001).

PATIENT CONTENT STATEMENT

Informed consent was obtained from all participants or from parents/ legal guardians in subjects under 18 years prior to entering this study, and the anonymity of the participants was ensured.

CLINICAL TRIAL REGISTRATION

N/A.

ORCID

Rikako Tsuji http://orcid.org/0000-0003-3122-9943

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.