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Monitoring neutrophil-to-lymphocyte ratio dynamics for personalized treatment in adolescent eating disorders: a retrospective cohort study

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Abstract

Objective This study aimed to evaluate the dynamics of the neutrophil-to-lymphocyte ratio (NLR) during the initial hospitalization of patients with eating disorders (EDs) and to assess its potential as a biomarker for monitoring disease severity and treatment response.

Methods A retrospective chart review was conducted with 55 patients aged ≤ 16 years diagnosed with anorexia nervosa or avoidant/restrictive food intake disorder and admitted to Jichi Medical University Hospital between 2015 and 2021. Sociodemographic and clinical characteristics including sex, age, rate of weight gain, percentage of ideal body weight (%IBW), tube feeding treatment, and NLR were obtained. Statistical analyses used a mixed model for repeated measures to assess NLR changes regarding %IBW and other clinical factors.

Results The NLR at admission was lower in the malnourished state but increased with weight recovery. MMRM revealed that tube feeding treatment ($\beta = 0.538$) and restoration of %IBW ($\beta = 0.029$) significantly predicted an increase in the NLR. The interaction between tube feeding and the quadratic term of %IBW was also significant, indicating distinct patterns of NLR changes: without tube feeding, NLR increased linearly with weight recovery, whereas with tube feeding, NLR exhibited a non-linear, upward-convex parabolic trend.

Discussion These findings suggest that NLR may offer an objective recovery marker less influenced by patient self-report. Monitoring NLR before and after tube feeding may help distinguish true physiological recovery from transient stress responses, providing complementary information to conventional assessments. Further research is warranted to establish its clinical relevance.

Keywords Neutrophil-to-lymphocyte ratio, Eating disorders, Tube feeding, Nutritional status, Ideal body weight

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Introduction

Eating disorders (EDs), psychiatric conditions manifesting in adolescence, lack established biomarkers for diagnosis or treatment. EDs involve significant disruptions in eating behaviors, leading to medical and psychological complications. Diagnosis is clinically assessed using operational diagnostic criteria, which include weight changes and symptoms, with the Diagnostic and Statistical Manual of Mental Disorders, 5th ed., as an example [1]. Therapists should also consider ancillary biomarkers such as hormones, neuroimaging, and re-feeding markers [2], though repeating these during treatment is costprohibitive. Unlike other psychiatric conditions, EDs are influenced by starvation and malnutrition, complicating the use of biomarkers for other mental health disorders [3]. Since the heterogeneity of EDs poses challenges in evaluating recovery based on single indicators, such as weight or psychopathological findings, a comprehensive assessment that incorporates multiple related factors could better capture the complexity of recovery. Developing a multimodal predictive model integrating such factors would be clinically valuable for improving personalized treatment and monitoring outcomes in patients with EDs.

Recently, the neutrophil-to-lymphocyte ratio (NLR) has gained attention as a biomarker for psychiatric disorders [4]. The NLR, derived from routine blood tests, is the ratio of neutrophils to lymphocytes. Neutrophils indicate innate immunity through inflammatory factors, whereas lymphocytes represent adaptive immunity, with low counts indicating compromised health and stress [5]. Elevated NLR is associated with acute episodes and disease severity in various adolescent psychiatric conditions [6-14]. However, in EDs, particularly anorexia nervosa (AN), NLR behaves differently [15-17]. Studies have shown that NLR decreases during acute AN, reflecting the body's starvation response [16, 17]. As patients recover, the NLR increases, indicating an improved nutritional and inflammatory status. NLR dynamics during ED treatment and their correlation with clinical features remain underexplored.

This study evaluated NLR trajectories in adolescent ED patients during initial hospitalization to assess their potential as biomarkers. We retrospectively analyzed NLR fluctuations in patients hospitalized for their first ED episode, associating these changes with clinical characteristics to determine NLR's reliability for monitoring disease severity and treatment response.

Materials and methods

A retrospective chart review was conducted with all patients admitted to the psychiatric ward of Jichi Medical University Hospital Tochigi Children's Medical Center between January 1, 2015, and December 31, 2021. This ward is the only inpatient child psychiatry unit in the region, which has a population of approximately 1.9 million. During the study period, all adolescents who required inpatient care for eating disorders were admitted here, which could minimize selection bias. Admission criteria were consistently applied, typically including patients with insufficient oral intake or those requiring physical stabilization. Therefore, the study sample is likely representative of adolescents with severe eating disorders requiring inpatient treatment in this geographic area. The diagnosis was verified by two trained child psychiatrists based on the DSM-5 criteria for AN or avoidant/restrictive feeding and intake disorder (ARFID).

Participants and inpatient treatment

This study included children with AN or ARFID who received initial inpatient ED treatment. The exclusion criteria were as follows: (i) age over 16 years, (ii) admission weight over 85% of ideal body weight (%IBW), and (iii) inability to measure the NLR at least twice. To maintain a clinically homogeneous sample of patients with significant undernutrition, we excluded individuals with an admission %IBW over 85%, based on clinical conventions commonly used in the world to identify significant undernutrition, although DSM-5 does not specify a numerical cutoff.

Inpatient treatment occurred in a closed child psychiatry ward managed by a multidisciplinary team of 3-4 child psychiatrists, psychologists, nurses, psychiatric social workers, and dieticians. This approach included establishing therapeutic relationships, diagnosis, assessment, psychoeducation, nutritional guidance, food records, re-nutritional therapy using behavioral techniques, and supportive psychotherapy. Psychiatrists met patients at least three times a week to discuss treatment plans, with periodic family interviews to share progress. Nurses provided dietary and lifestyle care and explained the disease stages. The psychologists conducted individual and group therapy sessions. Psychiatric social workers liaised with schoolteachers and offered social support for future school reintegration. Dietitians offered nutritional guidance. Re-nutritional therapy primarily involved oral nutrition with tube feeding if necessary. Tube feeding was initiated when patients were unable to maintain full oral intake for several days. Caloric intake was gradually increased by 100-200 kcal per week, aiming for 0.5 kg/ week weight gain.

Measurements

Sociodemographic and clinical characteristics

This study aimed to evaluate NLR dynamics in the inpatient treatment process and its association with sociodemographic and clinical characteristics. We examined the participants' sociodemographic and clinical characteristics to identify potential confounding factors: age at admission, sex, classification of eating disorders (AN, ARFID), duration of hospital stay, %IBW on admission, %IBW at discharge, rate of weight gain (kg/week), and gastric tube feeding. We excluded NLR values if the patient had a recorded temperature \geq 38 °C on the same calendar day as the blood draw. Three values were excluded by this criterion.

Percentage of ideal body weight (%IBW)

%IBW was calculated via a formula (patient weight × 100/ standard weight), where the standard weight was determined by the Japan Pediatric Endocrine Society's criteria [18]. Patients with <85%IBW were defined as having low body weight according to the Hirata method commonly used in Japan to evaluate pediatric physiques.

Statistical analysis

Statistical analysis examined the correlation between changes in NLR and other variables. NLRs at \geq 38 °C were excluded because of potential infectious disease effects. A paired t-test was used to compare %IBW at admission and discharge. Given the expected non-linear relationship between NLR and %IBW influenced by physical and psychological stress during inpatient treatment, a quadratic term for %IBW (%IBW²) was included in a mixed model for repeated measures (MMRM) analysis. To model the nonlinear association between %IBW and NLR, we tested various functional forms including quadratic, cubic, logarithmic, and spline terms. The quadratic form yielded the most interpretable and parsimonious model with comparable or superior fit. To prevent multicollinearity between %IBW and %IBW², %IBW was centered using grand-mean centering. An MMRM analysis incorporating a random slope model for %IBW was used to account for individual variations in its effect on NLR. Multicollinearity was checked using variance inflation factors (VIFs), with a cutoff of 2.5. Residual diagnostics, including residual and Q-Q plots, were conducted to assess the assumptions of normality and homoscedasticity. Heterogeneous residual variances were modeled and compared using likelihood ratio tests to address heteroscedasticity. Finally, model fit was evaluated using Akaike Information Criterion (AIC), along with marginal and conditional R² to assess explanatory power at both fixed and random levels. All analyses were performed with R software (version 4.4.1), and graphs were created using RStudio (2024.04.2+764).

Results

In this study, 76 patients were admitted to our hospital for treatment of eating disorders. Among them, two, three, and 16 were excluded because they were older, overweight, and had < 2 NLR measurements, respectively. A total of 55 patients were included in the study (Fig. 1). The clinical characteristics of the patients are shown in Table 1. A paired t-test revealed that %IBW was significantly higher at discharge than at admission (p < 0.01, data not shown). The frequency of NLR measurements decreased over time: 2.07 times per patient in the first week, 1.25 times in the second week, and below 1.0 per week thereafter. This trend is consistent with routine clinical practice.

Table 2 presents the findings of the MMRM analysis and identifies several predictors of NLR variability. Model 1 was fitted to examine the effects of tube feeding treatment, age in months, %IBW, %IBW², rate of weight gain (kg/week), gender, and diagnosis (AN or ARFID) on the NLR. Fixed effects estimates indicated that tube feeding had a statistically significant effect (β =0.538, p=0.007), with higher NLR values observed in the tube feeding group. The effect of the %IBW was statistically significant (β =0.029, p <. 0.001). %IBW² was also significant (β = -0.001, p=0.003), indicating a non-linear relationship between %IBW and NLR, characterized by an upward-convex parabolic trend.

To investigate the interactions between tube feeding and %IBW, variables that were statistically significant in model 1 were included in model 2. No interaction was found between tube feeding and %IBW, but an interaction emerged between tube feeding and %IBW² (β = -0.002, *p*=0.013), indicating that the NLR increased linearly without tube feeding and non-linearly with tube feeding, following an upward-convex parabolic trend. Random effects analysis revealed a standard deviation of 0.524 for random intercepts, which indicated variability in the baseline NLR among individuals. The standard deviation for the random slopes of %IBW² was 0.021, which suggests minimal variability in the effect of %IBW on the NLR.

To evaluate model fit and assumptions, we conducted a comprehensive diagnostic procedure. Residual plots and Q-Q plots revealed only minor deviations from normality and homoscedasticity, which were considered acceptable for linear mixed-effects models. VIFs were all below 2.5, indicating no substantial multicollinearity among the predictors, including interaction and quadratic terms. To account for heteroscedasticity across tube feeding conditions, we modeled group-specific residual variances using a heterogeneous variance structure. This approach significantly improved model fit in both models, as confirmed by likelihood ratio tests (p < 0.0001).

To compare model performance, we used AIC, marginal R^2 , and conditional R^2 . For Model 1 (without interaction terms), the AIC was 1253.2, the conditional R^2 was 0.426, and the marginal R^2 was 0.142. For Model 2 (including interaction terms between %IBW and tube feeding), the AIC was slightly higher at 1257.3, with a

Consort flow diagram of patients



EDs: eating disorders, NLR: neutrophil-to-lymphocyte ratio

Fig. 1 Consort flow diagram of patients

conditional R² of 0.384 and marginal R² of 0.085. These results suggest that Model 1 achieved a better balance of explanatory power and parsimony. Additionally, based on the observed t-value for %IBW (t=3.75), an approximate effect size of f² = 0.265 was calculated, indicating a medium-to-large effect according to Cohen's criteria. This supports the adequacy of the sample size for detecting clinically meaningful associations in this mixedeffects modeling context.

Discussion

Changes in NLR in adolescent ED patients during inpatient treatment indicated that body weight recovery was crucial for restoring NLR values. As body weight increased, NLR values progressively normalized, highlighting the importance of physical health in stabilizing inflammatory markers. MMRM analysis showed a linear NLR increase without tube feeding, reflecting gradual recovery with weight gain, and a nonlinear, upward-convex trend with tube feeding, suggesting accelerated weight gain but additional stressors affecting the NLR. The initial NLR values varied significantly among participants; however, the impact of %IBW on NLR was consistent, regardless of the initial NLR values. This indicates that weight restoration is essential for improving NLR values, irrespective of the baseline immune status or social background, as evidenced by the upward NLR trend during treatment.

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Variables	N (%)
Sex	
Female	50 (90.9)
Male	5 (9.1)
Diagnosis (AN)	
AN	47 (85.5)
ARFID	8 (14.5)
Tube feeding treatment (Yes)	
Yes	22 (40.0)
No	33 (60.0)
Race	
Japanese	55 (100)
	Mean (SD)
Age on admission (months)	154.5 (21.2)
Length of hospital stay (days)	104.8 (53.8)
%IBW on admission	71.9 (6.2)
%IBW at discharge	87.1 (10.0)
rate of weight gain (kg/week)	0.489 (0.331)
NLR on admission	1.44 (0.68)

Table 2 Mixed model for repeated measure

Model 1 (Marginal R ² : 0.142, Conditional R ² : 0.426)					
Fixed effect					
Parameters	Estimate	SE	t	p-value	
Intercept	0.380	0.741	0.513	0.608	
Tube feeding (No)	0.538	0.190	2.834	0.007	
%IBW	0.029	0.008	3.750	< 0.001	
%IBW ²	-0.001	0.0004	-2.962	0.003	
Age (months)	0.006	0.004	1.304	0.198	
Gender (Women)	0.457	0.365	1.252	0.216	
Diagnosis (AN)	-0.040	0.306	-0.130	0.897	
Weight gain rate (kg/week)	0.459	0.275	1.666	0.102	
Random effect					
Parameters	SD	Correlation			
Intercept	0.510				
%IBW	0.026	0.036			
Residual	0.797				
Model 2 (Marginal R ² : 0.085, Conditional R ² : 0.384)					
Fixed effect					

rinco enece				
Parameters	Estimate	SE	t	p-value
Intercept	1.579	0.112	14.042	< 0.001
Tube feeding (Yes)	0.434	0.176	2.463	0.017
%IBW	0.023	0.009	2.475	0.014
%IBW ²	-0.0003	0.0005	-0.662	0.508
Tube feeding × %IBW	0.008	0.014	0.557	0.578
Tube feeding \times %IBW ²	-0.002	0.001	-2.484	0.013
Random effect				
Parameters	SD	Correlation		
Intercept	0.524			
%IBW	0.021	0.352		
Residual	0.798			

A previous study reported that NLR tended to decrease during the acute phase of EDs, particularly AN, owing to decreased muscle mass, bone marrow activity, adiponectin levels, and cachexia [16, 17]. Our findings align with this, as the NLR values at admission were lower in malnourished patients. Importantly, as body weight improved during treatment, the NLR values also showed significant recovery, highlighting the interdependence of nutritional status and immune function. Tube feeding treatment in patients with EDs can elevate NLR, likely owing to both physical and psychological stress. The use of tube feeding in the treatment of EDs has been associated with shorter hospital stays and increased caloric intake, which can facilitate faster weight restoration [19]. Although generally considered safe, side effects, such as nasal irritation, epistaxis, and anxiety, are common. In some cases, physical restraint may be required; however, our study had no cases that required physical restraint. Additionally, tube feeding treatment may provoke feelings of fear or loss of control due to passive nutritional intake and faster weight restoration [20], potentially contributing to an elevated inflammatory response. Furthermore, the apparent elevation in NLR may have been due to physical irritation and mechanical stimulation associated with tube feeding, rather than reflecting true improvements in the underlying condition, because NLR tended to decrease in the late phase of inpatient treatment with tube feeding. The observed increase in NLR in patients receiving tube feeding may reflect physiological stress or localized inflammatory responses. However, as stress markers were not measured, this remains a hypothesis. Future studies should include markers such as cortisol or salivary alpha-amylase. Additionally, the decreasing trend in NLR following gastric tube removal may reflect the resolution of temporary inflammation or stress responses caused by the tube itself. However, since blood draws and tube feeding were not temporally coordinated in our dataset, we could not directly evaluate the short-term impact of tube feeding on NLR levels. Although localized inflammation due to nasogastric tube use may offer a plausible explanation, NLR may be particularly informative if assessed before and after tube feeding and at regular intervals during nutritional rehabilitation. Sustained normalization of NLR values may serve as an indicator of recovery. Therefore, careful monitoring of changes in NLR after discontinuation of tube feeding is crucial to better understand its true implications and to ensure that NLR dynamics genuinely indicate recovery rather than transient stress responses.

In this study, we examined NLR as a potential biomarker for evaluating recovery in patients with EDs. However, the complexity and heterogeneity of EDs necessitate a broader approach for recovery assessment [3]. Future research should incorporate a diverse range of variables, including clinical, biochemical, nutritional, and psychological factors into a unified predictive framework. The integration of these factors would provide a more holistic understanding of recovery dynamics and allow more nuanced assessments tailored to individual patients. Moreover, leveraging advanced methodologies such as machine learning and artificial intelligence could facilitate the development of robust multimodal predictive models. These models would not only improve the accuracy of recovery predictions but also support the implementation of personalized treatment strategies and optimize interventions for specific patient profiles. By addressing the multifaceted nature of EDs, this approach has the potential to significantly enhance the clinical utility and outcomes.

This study has several limitations. First, as a retrospective analysis, this research has inherent limitations including missing data, potential information bias due to non-standardized timing of measurements, and residual confounding. NLR was measured more frequently during early hospitalization, which may have led to underrepresentation of later phases. Although selection bias was minimized by including all eligible inpatients from a single regional center, the sample may still reflect more severe cases. In addition, individual variability in treatment decisions such as tube feeding initiation may have influenced outcomes. Furthermore, because we excluded patients with an admission %IBW over 85%, our sample may overrepresent more severely malnourished cases. Although this criterion ensured clinical homogeneity and alignment with diagnostic thresholds for anorexia nervosa and ARFID, it may limit the generalizability of our findings to adolescents with less severe or atypical presentations of eating disorders. Second, childhood maltreatment, which could influence NLR, was not evaluated. Future studies should assess patients' psychosocial backgrounds to better understand the impact of trauma on NLR fluctuations. Third, differences in tube feeding usage, including duration and methods, and the psychological effects of tube feeding were not considered. Fourth, tube feeding might have triggered hyperactivity in some patients, potentially elevating the neutrophil counts and NLR. This confounder was not assessed and requires further investigation. Future studies should examine the impact of psychosocial factors on immune function and explore the potential influence of tube feeding on inflammatory markers. Finally, this study lacks a priori power analysis to ascertain the optimal sample size. Although post hoc effect size estimation indicated that the association between %IBW and NLR was of medium-to-large magnitude ($f^2 \approx 0.265$), a formal power analysis was not conducted beforehand. This omission is attributed to the methodological complexity involved in power calculations for linear mixed-effects models, which encompass both fixed and random effects. Unlike traditional linear regression, mixed models do not have standardized methods for estimating power, particularly when dealing with repeated measures or hierarchical data structures. In this study, the NLR was highlighted as a component of a potential multimodal recovery index. As a quantitative metric, NLR offers valuable insights; however, future studies should aim to incorporate a variety of data types, including other quantitative measures and possibly non-quantitative data, such as imaging. This study advances personalized treatment in EDs by developing a more comprehensive recovery index.

Abbreviations

AN	Anorexia Nervosa
ARFID	Avoidant/restrictive feeding and intake disorder
DSM-5	Diagnostic and statistical manual of mental disorders. 5th ed.
EDs	Eating disorders
ICD-10	International statistical classification of diseases and related health
	problems, 10th Revision
MMRM	Mixed model for repeated measures
NLR	Neutrophil-to-lymphocyte ratio
%IBW	Percentage of ideal body weight

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Author contributions

Y.I. and T.Y. designed the study. Y.I., K.K. (Kurata), S.O., K.K. (Kurane), R.F., T.M., and H.N. collected the data. Y.M. provided financial support. Y.I., Y.O., T.Y., and S.S. prepared the original draft. Y.O. and T.Y. provided statistical analyses supports. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Review Committee of Jichi Medical University. Consent was obtained via an opt-out method, with information provided through documents posted on the websites of the Departments of Psychiatry and Children's Mental Health at Jichi Medical University, ensuring participants were adequately informed.

Consent for publication

This study was conducted as a retrospective chart review. Participation was based on an opt-out method, whereby eligible patients and their guardians were informed of the study through documents posted on the website of the Departments of Psychiatry and Children's Mental Health at Jichi Medical University. Individuals who did not wish to participate were given the opportunity to express their decision to opt out. As no personal identifiable information is included in this publication, additional written consent for publication was not required.

Competing interests

The authors declare no competing interests.

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