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ORIGINAL ARTICLE

Emergence agitation in open rhinoplasty operations neutrophil/lymphocyte and platelet/lymphocyte ratio as a predictive marker

Agitación de emergencia en operaciones de rinoplastia abierta: cocientes neutrófilos/linfocitos y plaquetas/linfocitos como marcadores predictivos

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Abstract

Objective: *We aimed to evaluate the relationship between emergence agitation and pre-operative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) after rhinoplasty.* **Methods:** *Our study included 104 patients. All patients underwent surgery under standard general anesthesia. In the pre-operative period, receiver operating curve analysis was performed to determine the cutoff values of NLR and PLR for the risk of emergence agitation and pre-operative anxiety. A correlation analysis was performed between NLR and PLR, the State-Trait Anxiety Inventory scale, and the body image disturbance scale.* **Results:** *While the area under the curve (AUC) value of NLR for emergence agitation was not significant (p = 0.76), the cutoff value for PLR was 113.37 (AUC = 0.624, sensitivity = 80.65%, specificity = 45.21%, p = 0.046). Median PLR values were higher in patients with emergence agitation (p = 0.046). The AUC value for pre-operative anxiety was not significant. There was no correlation between NLR and PLR and the scales assessed.* **Conclusions:** *We suggest that PLR may be a predictive biomarker in evaluating the risk of pre-operative emergence agitation in patients scheduled for rhinoplasty.*

Keywords: Emergence agitation. Neutrophil-lymphocyte ratio. Platelet-lymphocyte ratio. Anxiety. Body dysmorphic disorder.

Resumen

Objetivo: *Evaluar la relación entre la agitación de emergencia y los cocientes preoperatorios neutrófilos/linfocitos (NLR) y plaquetas/linfocitos (PLR) tras una rinoplastia.* **Métodos:** *En el estudio participaron 104 pacientes, todos ellos sometidos a cirugía bajo anestesia general estándar. En el periodo preoperatorio se realizó un análisis de curva operativa del receptor para determinar los valores de corte de NLR y PLR para el riesgo de agitación de emergencia y de ansiedad preoperatoria. Se realizó un análisis de correlación entre NLR y PLR, la Escala de Ansiedad Estado-Rasgo y la Escala de Alteración de la Imagen Corporal.* **Resultados:** *Mientras que el valor del área bajo la curva (AUC) de NLR para la agitación de emergencia no fue significativo (p = 0.76), el valor de corte para PLR fue de 113.37 (AUC = 0.624, sensibilidad del 80.65% y especificidad del 45.21%; p = 0.046). Los valores medios de PLR fueron mayores en los pacientes con agitación de emergencia (p = 0.046). El valor del AUC para la ansiedad preoperatoria no fue significativo. No hubo correlación entre NLR y PLR y las escalas evaluadas.* **Conclusiones:** *Sugerimos que el PLR puede ser un biomarcador predictivo en la evaluación del riesgo de agitación de emergencia preoperatoria en pacientes programados para rinoplastia.*

Palabras clave: Agitación de emergencia. Cociente neutrófilos/linfocitos. Cociente plaquetas-linfocitos. Ansiedad. Trastorno dismórfico corporal.

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Introduction

Emergence agitation is defined as a state of psychomotor excitement that occurs before full emergence of consciousness after general anesthesia and is self-limiting within 5-15 min[1]. Its incidence has been reported to reach approximately 50% after facial surgeries such as ear-nose-throat and orthognathic procedures[2,3].

Pathophysiologically, it has been reported that it may occur as a result of sympathetic activation secondary to inadequate analgesia or mental disorders that trigger neuroinflammation[2,4]. Etiologic factors include post-operative pain, pre-operative anxiety, young age, type of surgery, anesthetic agent used, and psychic problems[5,6].

Especially recently, rhinoplasty has become the main esthetic operation performed by half a million people a year to improve the appearance of the nose[7]. In a literature review, a history of plastic surgery was found to be associated with a high level and incidence of anxiety[8]. In rhinoplasty surgery, which is not only a technical procedure, body dysmorphic disorder (BDD) is one of the factors that are important in determining the person's mood and affect post-operative satisfaction[9]. Even if the existing defect is small, obsession and anxiety about it are excessive[10].

Neuroinflammation is emphasized as the main factor in the pathophysiology of emergence agitation, anxiety disorders, and obsessive-compulsive-related disorders. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are neurobiological markers, are accepted as easily measurable and low-cost parameters reflecting the inflammatory state[11].

NLR and PLR are affected by the presence of systemic pathologies, including malignancies and various diseases such as mood disorders[12]. An association between NLR and PLR and diseases in which neuroinflammation plays a role in pathophysiology, such as mood disorders, anxiety disorders, and schizophrenia, has been demonstrated[13-16]. Although there are studies in the literature on the relationship between NLR and PLR with neuropsychiatric disorders such as major depressive disorder, schizophrenia, and obsessive-compulsive disorder (OCD), no study was found to be related to emergence agitation, pre-operative anxiety, State-Trait Anxiety Inventory (STAI) scale, and BDD scale.

The primary aim of our study was to investigate the relationship between NLR and PLR levels, which are neurobiological markers, and emergence agitation in adult patients with post-operative emergence agitation. The secondary aim was to evaluate the relationship between neurobiological markers (NLR and PLR) and pre-operative anxiety, STAI scale, and BDD scale scores.

Methods

Our study was prospectively conducted on a total of 104 patients with American Society of Anesthesiologists (ASA) risk classification I and II, 18-45 years of age, who underwent open rhinoplasty surgery by Plastic Reconstructive and Esthetic Surgery after approval of the local ethics committee of Karadeniz Technical University Faculty of Medicine (protocol number: 2021/374), and whose written and verbal informed consent was obtained after verbal information about the study.

Body mass index > 30 kg/m^2, allergy to induction agent(s) and opioid, chronic pain medication, active infection, autoimmune, cardiovascular, gastrointestinal and neurological diseases, renal or hepatic insufficiency, chronic respiratory pathology, malignancy diagnosis (colorectal, gastric, pancreatic, esophageal, lung, gynecologic, etc.), history of chronic systemic diseases (hypertension and diabetes mellitus), hematologic (leukocyte and platelet) diseases, non-cooperative patients and patients with physical and verbal comparison.), patients with a history of chronic systemic diseases (hypertension and diabetes mellitus), patients with hematologic (leukocyte and platelet) diseases, patients who were unable to cooperate, and patients who were physically and verbally incapable of comparison were excluded.

In our study, demographic data (age, gender, ASA score, presence of surgical history, duration of surgery, and duration of anesthesia), pre-operative measurements (STAI-I and II scale) scores, body image disturbance questionnaire (BIDQ) score, presence of pre-operative anxiety, laboratory variables (NLR and PLR), and post-operative emergence agitation were recorded.

NLRs and PLRs were manually calculated using absolute values from the patient's complete blood count (absolute and relative values of leukocytes, neutrophils, lymphocytes, and platelets) requested by the relevant branch before the operation.

After an adequate pre-operative fasting period, patients who came to the operating room were monitored non-invasively for arterial pressure, heart rate (HR), electrocardiogram, peripheral oxygen saturation, end-tidal carbon dioxide, and bispectral index values (BIS) during anesthesia monitoring. Anesthesia induction was performed with intravenous (IV) 1μg/kg fentanyl, 3 mg/kg propofol, and 0.6 mg/kg rocuronium for muscle relaxation in all patients included in our study. Anesthesia maintenance was achieved by inhalation anesthesia with sevoflurane (minimum alveolar concentration 1-1.5) and 1:1 O_2/Air with a BIS value of 40-60 and remifentanil infusion (0.01-0.2 μg/kg/min). Near the end of the operation, all patients received IV 1 g paracetamol and 50 mg tramadol for post-operative analgesia as standard.

Open rhinoplasty surgeries performed on all patients participating in the study were performed by the same Plastic Reconstructive and Esthetic Surgery specialist, and the same internal nasal splints (Eon Meditech internal nasal airway splint standard, silicone, double hole) were used.

Emergence agitation after extubation and in the post-anesthesia care unit was evaluated with the Richmond agitation sedation scale (RASS) (+ 1 to + 4: anxiety or agitation, 0: calm and awake, –1 to –5: sedated, –5: not arousable). Patients with a RASS score ≥ 2 were considered to have developed emergence agitation[17].

Pre-operative anxiety was considered to be present in patients with an STAI-I score of 30 and above, which was used to evaluate the level of state anxiety in the pre-operative period[18].

Patients' concerns about their general body image and bodily concerns in social life were evaluated with the body image disorder scale questionnaire (1: none, 2: mild, 3: moderate, 4: severe, and 5: extreme)[19]. High values indicated a negative body perception and a severe negative effect of this perception on psychosocial functions, whereas low values were interpreted as no disturbing problem in body image.

Statistical analysis

The data were analyzed using IBM Statistical Package for the Social Sciences Statistics v23. Compliance with normal distribution was examined by the Shapiro–Wilk and Kolmogorov–Smirnov tests. Categorical data by groups were compared using the χ^2, Yates' correction, and Fisher's exact tests. An Independent two-sample t-test was used to compare normally distributed data, and the Mann–Whitney U-test was used to compare non-normally distributed data. The relationship between non-normally distributed quantitative data was analyzed by Spearman's ρ correlation. The point biserial correlation coefficient was used to examine the relationship between quantitative data and two-group categorical data. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff value of the parameters for agitation and pre-operative anxiety. The analysis results were presented as mean ± SD and median (minimum-maximum) for quantitative data and frequency (percentage) for categorical data. The significance level was taken as $p < 0.05$.

Results

One hundred four patients who underwent open rhinoplasty surgery and met the inclusion criteria were included in the study. The patients' demographic data and clinical characteristics are shown in table 1.

Pre-operative anxiety (STAI-I ≥ 30) was detected in 85.58% (n: 85) of the participants, whereas emergence agitation (RASS ≥ + 2) was observed in 29.81% (n: 31) in the post-operative period.

ROC analysis was performed to determine the usefulness of NLR and PLR as predictive markers in determining emergence agitation and pre-operative anxiety (Table 2).

While the AUC value of NLR cutoff value for emergence agitation was not statistically significant (p = 0.76), the cutoff value for PLR was 113.37 (AUC = 0.624, sensitivity = 80.65%, specificity = 45.21%, positive predictive value (PPV): 38.46%, negative predictive value (NPV): 84.62%, p = 0.046) (Fig. 1). The change in PLR values according to the presence of emergence agitation is shown in Fig. 2. The median PLR values were statistically significantly higher in patients with emergence agitation than those without (135.9 vs. 120.97, p = 0.046), respectively.

The AUC value of NLR and PLR cutoff value for pre-operative anxiety was not statistically significant (p = 0.08; 0.33) (Fig. 3).

The relationship between NLR and PLR, and STAI I-II and BIDQ is shown in table 3, and no statistically significant difference was found (p > 0.050).

Discussion

As a result of our study, PLR in the pre-operative period is a predictive biomarker in assessing the risk of emergence agitation. In addition, NLR and PLR

Table 1. Demographic data and laboratory parameters

Variables	Total (n = 104)
Gender	
Female	65 (62.5)
Male	39 (37.5)
Age	28.18 ± 9.14
ASA score	
ASA 1	58 (55.8)
ASA 2	46 (44.2)
Education level	
Primary school	10 (9.6)
High school	39 (37.5)
University	55 (52.9)
Duration of anesthesia (min)	66.39 ± 15.00
Duration of surgery (min)	53.47 ± 14.34
Neutrophil count (× 10^3/μL)	4.25 ± 1.50
Lymphocyte count (× 10^3/μL)	2.25 ± 0.63
Platelet count (× 10^3/μL)	272.89 ± 59.65
NLR	1.99 ± 0.82
PLR	129.60 ± 47.00
STAI-I score	37.21 ± 8.32
STAI-II score	39.03 ± 7.88

Frequency (percentage), mean ± SD.
ASA: American Society of Anesthesiologists; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; STAI-I: state anxiety scale; STAI-II: trait anxiety scale; Min: minute.

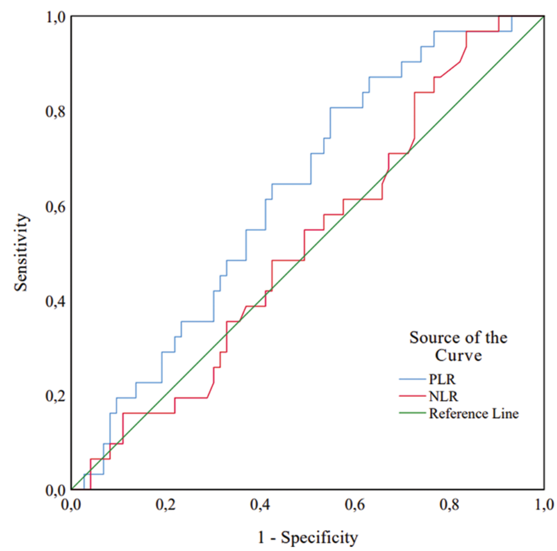

Figure 1. *ROC curve of PLR and NLR values for emergence agitation state*

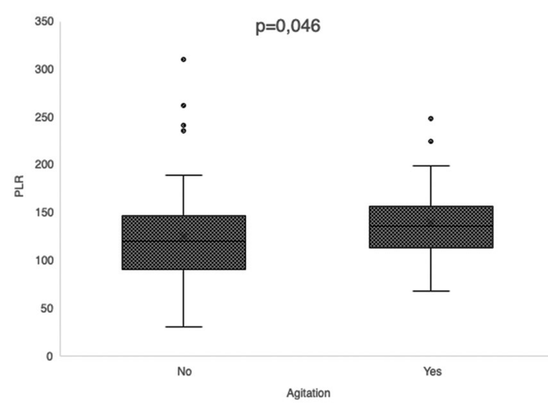

Figure 2. *Change in PLR values according to the presence of emergence agitation*

were not associated with pre-operative anxiety, STAI scale score, and BDD scale score.

Emergence agitation is a state of hyperactivity that occurs during recovery of consciousness during awakening from general anesthesia. Two mechanisms are generally emphasized in its pathophysiology. The first is sympathetic activation secondary to stimuli due to inadequately treated nociception, and the second is neuroinflammatory mechanisms because it is more common postoperatively in patients with higher inflammatory mediators (interleukin-6, tumor necrosis factor-α, and T and B lymphocytes) and endogenous catecholamine levels[1,20,21].

Stress and severe diseases may increase cortisol levels, activating neutrophil count and increasing lymphocyte apoptosis due to hypothalamic-pituitary-adrenal (HPA) axis activation[22]. While neutrophil production from the bone marrow increases, lymphopenia occurs[23]. This leads to an increase in NLR. Similarly, both stress and inflammatory factors increase platelet count, leading to high PLR levels in a lymphopenic environment[24].

NLR and PLR are frequently used to determine the severity of inflammation because of their low cost and easy applicability. Various cutoff values of NLR and PLR have been determined as prognostic or predictive biomarkers[25-27].

A study conducted in open rhinoplasties found that NLR > 2.1 was associated with severe post-operative edema, and NLR > 1.5 was associated with severe post-operative ecchymosis[28]. In this study, only a cut-off value for NLR was obtained, and PLR was not used as a prognostic or predictive biomarker, which can be considered a study limitation.

Table 2. ROC analysis result of NLR and PLR values for emergence agitation and pre-operative anxiety

Variables	Cutoff value	AUC (95% CI)	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Emergence agitation							
NLR		0.519 (0.402-0.636)	0.763				
PLR	≥ 113.37	0.624 (0.513-0.735)	**0.046***	80.65	45.21	38.46	84.62
Pre-operative anxiety							
NLR		0.641 (0,494-0.787)	0.082				
PLR		0.578 (0.428-0.727)	0.338				

*p < 0.05. AUC: area under curve; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PPV: positive predictive value; NPV: negative predictive value.

Table 3. Relationship between NLR and PLR, and STAI I-II and BIDQ

Variables	NLR		PLR	
	r	p	r	p
STAI-I score	0.130	0.189	0.104	0.291
STAI-II score	–0.034	0.733	0.086	0.384
BIDQ score	0.129	0.192	0.004	0.972

r: spearman's ρ correlation coefficient; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; STAI-I: state anxiety scale; STAI-II: trait anxiety scale; BIDQ: body image disorder questionnaire.

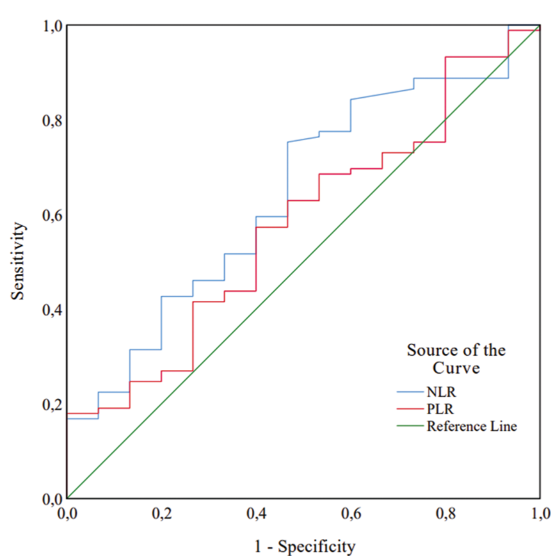

Figure 3. *ROC curve of NLR and PLR values for preoperative anxiety status.*

The role of autoimmunity and inflammation in neurocognitive pathophysiology has been the subject of many studies[29,30]. Dysregulated cognitive activation contributes to systemic inflammation in relation to HPA axis dysregulation[31]. In a review, anxiety disorders were found to be associated with chronic systemic inflammation[32].

In the central nervous system, serotonin is involved in the pathophysiology of anxiety disorders and the regulation of platelet function[33]. It is also known that peripheral platelets reflect serotonergic function when the central nervous system is inaccessible[34]. In addition, platelet activation stimulated by serotonin plays an active role in neurocognitive pathophysiology, leading to anxiety[35,36].

Experimental studies have shown that triggered stress causes inflammation and that inflammation may occur, especially in anxiety disorders secondary to acute stress[37,38]. At the same time, different studies on animals have shown that inflammation activates the limbic regions of the brain and leads to anxiety and avoidance behaviors[39,40].

In a study conducted on adolescents, it was reported that PLR (> 127.5) may indicate an increased risk of suicidality[41]. It has been reported that PLR may be more significant than NLR in patients with major depressive disorder and suicide attempts[42]. In addition, PLR was associated with the severity of major depressive disorder, especially with the psychotic process[43]. In another study, PLR was found to be an independent predictor of manic episodes[44].

In a study evaluating the risk of post-operative delirium in patients scheduled for vascular surgery, cutoff values of NLR > 3.57 and PLR > 139.2 were associated with an increased incidence of post-operative delirium[45]. High PLR values (>100) in patients admitted to the intensive care unit were reported as an independent risk factor for delirium and found to be associated with a high incidence of delirium[46].

In the literature, we did not find any study investigating the relationship between NLR and PLR and emergence agitation, pre-operative anxiety, STAI scale scores, and BDD scale scores.

Our study investigated whether pre-operative NLR and PLR are predictive markers secondary to neuroinflammation in determining the risk of post-operative emergence agitation. As a result of our data analysis, the PLR cutoff value (113.37) was found for emergence agitation but not for NLR. Our results were consistent with the studies in the literature investigating the relationship between different psychiatric disorders and neurobiological markers. It was concluded that the significant elevation of PLR in our study was due to neuroinflammatory mechanisms in the development of emergence agitation and stress-induced HPA axis dysregulation.

BDD was included in the obsessive-compulsive and related disorders section of the Diagnostic and Statistical Manual of Mental Disorders-5 due to similarities with OCD, including repetitive behaviors[47]. In the literature, it was observed that patients with BDD who wanted to undergo cosmetic surgery were more depressed and anxious and showed frequent compulsive behaviors, resulting in excessive mental activity[48].

In a study, it was observed that chronic inflammation caused neuronal activity changes in the anterior cingulate cortex and prefrontal cortex associated with OCD[49]. In another study, it was observed that NLR and PLR values were significantly higher in adolescents with OCD and anxiety disorders compared to those with OCD alone, and it was stated that this may be the result of increased inflammatory response secondary to more irregular cognitive actions[50].

In our study, no correlation was detected between BDD scale scores and NLR, PLR, and trait anxiety scores. We attribute this to the fact that the participants were less obsessed with the nasal structures due to the region-specific nasal anatomy and, as a result, did not trigger sufficient inflammatory processes. In addition, the results of the diagnostic tests applied in the pre-operative period and used to determine both STAI level and BDD may vary according to the intellectual characteristics of the participants. As a result, the relationship between scoring systems and neurologic biomarkers cannot be determined effectively. For this reason, it may be more appropriate to use a biomarker such as PLR, which is frequently used in the literature and has high reliability in evaluating emergence agitation.

Limitations

The current study has some limitations. Regarding the current study, emergence agitation risk factors were not primarily evaluated. Concomitant proinflammatory mediators were not examined. The current study used self-report scales and was completed over a long period of time. Participants were not subjected to additional psychiatric evaluation. In addition, it can be considered a limitation that participants with a history of smoking and antidepressant use, which affect biomarker rates, should not be excluded from the study as a limitation.

Conclusions

Our study shows that PLR > 113.37 is associated with emergence agitation in patients undergoing open rhinoplasty. Clinicians can use pre-operative PLR as a predictive neurobiological marker to evaluate emergence agitation risk in patients scheduled for open rhinoplasty surgery. This way, the risk of emergence agitation can be reduced by taking necessary precautions. Additional prospective studies should be conducted to confirm our findings.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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