Article

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Constructing a Multivariate Predictive Model for Postoperative 90-Day Depression Risk in Non-Small Cell Lung Cancer Based on Preoperative Peripheral Blood NLR, LMR, and PLR

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Background: Depression represents a significant clinical concern for individuals diagnosed with non-small cell lung cancer (NSCLC) following surgical resection. This study aimed to investigate the potential of preoperative peripheral blood parameters, including the neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR), as predictive indicators for the risk of developing depression within the initial 90-day postoperative period in NSCLC patients.

Methods: A prospective cohort study was conducted, enrolling 350 NSCLC patients, with 250 participants in the training set and 100 participants in the testing set. Participants were classified based on the presence or absence of depression 90 days after surgery. Preoperative blood parameters, including NLR, LMR, PLR, and inflammatory biomarkers, were measured. Statistical analyses, encompassing Logistics regression analysis and receiver operating characteristic (ROC) curve analysis, were performed to assess the significance and predictive value of these blood parameters. Multivariate predictive models were constructed based on the identified significant parameters.

Results: In the training set, statistically significant differences were observed between the non-depression and depression groups for NLR (4.35 $\pm$ 1.23 vs. 3.14 $\pm$ 0.82, t = 8.715, $p < 0.001$), LMR (3.84 $\pm$ 1.58 vs. 5.58 $\pm$ 1.23, t = 8.849, $p < 0.001$), PLR (187.46 $\pm$ 35.26 vs. 152.36 $\pm$ 32.46, t = 7.112, $p < 0.001$), and various blood parameters. Logistics regression analysis showed significant associations between NLR, LMR, PLR, and postoperative depression. ROC curve analysis indicated the predictive value of NLR [area under the curve (AUC) = 0.794], LMR (AUC = 0.800), and PLR (AUC = 0.766), with the multivariate model yielding an AUC of 0.931. These results were consistent in the testing set, where significant differences were observed between the non-depression and depression groups for NLR (4.23 $\pm$ 1.24 vs. 3.13 $\pm$ 0.75, t = 5.417, $p < 0.001$), LMR (3.17 $\pm$ 1.55 vs. 4.76 $\pm$ 1.22, t = 5.412, $p < 0.001$), PLR (189.46 $\pm$ 46.58 vs. 151.48 $\pm$ 34.26, t = 4.481, $p < 0.001$), and various blood parameters. The AUC values were 0.771, 0.791, and 0.755 for NLR, LMR, and PLR, respectively, while the multivariate model yielded an AUC of 0.928.

Conclusions: The study highlights the potential of preoperative peripheral blood NLR, LMR, and PLR as predictive indicators for the risk of postoperative 90-day depression in patients with NSCLC.

Clinical Trial Registration: Approval number: ChiCTR2300070375, https://www.chictr.org.cn/index.html.

Keywords: multivariate predictive model; postoperative 90-day depression risk; NSCLC; NLR; LMR; PLR

Introduction

Lung cancer, predominantly the non-small cell lung cancer (NSCLC) subtype accounting for approximately 85% of cases, is a leading cause of cancer-related mortality worldwide [1]. Surgical resection remains a pivotal curative treatment modality for early-stage NSCLC, offering the potential for long-term survival and disease control [2]. However, the postoperative period poses significant challenges for patients, encompassing the physical and psychological impact of the diagnosis, treatment, and recovery process.

Patients with NSCLC exhibit a high prevalence of depressive symptoms, with an estimated 36% experiencing moderate to severe depression at the time of diagnosis. This clinical presentation is often resistant to psychological treatment [3]. The prevalence of depression in cancer patients, particularly those undergoing surgical procedures, has garnered increasing attention due to its detrimental effects on overall well-being, treatment adherence, and clinical outcomes [4–6]. Postoperative depression in NSCLC patients can manifest as persistent feelings of sadness, hopelessness, and reduced quality of life, adding a layer of complexity

to their recovery journey [7,8]. Identifying individuals at higher risk for postoperative depression is crucial for implementing timely interventions and personalized support strategies to mitigate its impact on patient outcomes.

Depression is associated with biological dysregulation that may contribute to disease progression. Lung cancer is characterized by a dysfunctional immune system, as evidenced by tobacco/smoking-induced inflammation, an inflammatory tumor microenvironment, and robust, systemic inflammatory responses [9]. In this context, there is evidence that severe depressive symptoms are correlated with elevations of proinflammatory cytokines, decreased adaptive immune responses, and others [10]. Thus, findings suggest that inflammation with depression co-occurs with that arising from lung cancer [11].

The relationship between cancer-related inflammation and depressive symptoms has garnered significant attention in recent years [12–14]. Accumulating evidence suggests a crucial interplay between the immune system and the central nervous system in the pathogenesis of depressive symptoms. Pro-inflammatory cytokines and immune dysregulation contribute to the neurobiological changes observed in depression [15,16]. Consequently, investigating peripheral blood parameters associated with systemic inflammation, such as the neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR), has emerged as a promising approach for predicting postoperative depression risk in cancer patients [17]. NLR, LMR, and PLR have emerged as readily available and cost-effective markers of systemic inflammation, reflecting the balance between pro-inflammatory and anti-inflammatory processes in the body [18]. These blood parameters have been studied in various clinical contexts, including cancer, cardiovascular disease, and inflammatory conditions, demonstrating their potential as prognostic and predictive indicators for patient outcomes. In the context of cancer, elevated NLR decreased LMR, and increased PLR have been associated with tumor progression, treatment response, and survival outcomes across different malignancies. These associations underscore the relevance of NLR, LMR, and PLR as indicators of the tumor microenvironment and host immune response.

While the prognostic value of NLR, LMR, and PLR in cancer has been extensively studied, their potential utility in predicting postoperative depression risk among NSCLC patients remains relatively unexplored. Early identification of individuals at higher risk for postoperative depression could facilitate targeted monitoring and supportive interventions, potentially improving clinical outcomes and patient well-being. Therefore, this study aims to investigate the association between preoperative peripheral blood NLR, LMR, and PLR and the risk of postoperative depression in NSCLC patients undergoing surgical resection.

Materials and Methods

Research Object

The study design was a prospective cohort study. The recruitment plan aimed to enroll 350 participants from Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) between October 2022 and October 2023. Participants were classified into two groups based on their depression status 90 days after undergoing curative lung cancer surgery: those who did not develop postoperative depression and those who did. Subsequently, the participants were randomly allocated into a training set comprising 250 individuals and a testing set comprising 100 individuals, adhering to a 7:3 ratio.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients diagnosed with NSCLC who have undergone complete surgical resection; (2) tumor stage I–II; (3) pathological type of squamous cell carcinoma or adenocarcinoma; (4) age >18 years; (5) completion of follow-up assessment at 90 days postoperatively; (6) completion of depression screening and evaluation during the outcome interview; and (7) availability of complete medical records.

Exclusion criteria: (1) severe medical history; (2) factors that may affect white blood cell, lymphocyte, and platelet counts, such as the history of infection, concomitant hematologic or autoimmune diseases; (3) patients with two or more primary malignant tumors; (4) mortality within 90 days postoperatively; (5) acute cerebrovascular events, traumatic brain injury, or other central nervous system disorders within 90 days postoperatively; (6) patients with acute cardiac disease or chronic underlying diseases; (7) patients with severe liver or kidney impairment; and (8) patients with a history of mental illness.

Case withdrawal and dropout: All enrolled participants possess the right to withdraw from the study at any time. Reasons for withdrawal: (1) participant's request to withdraw and unwillingness to continue; (2) loss to follow-up; (3) refusal to continue the follow-up; and (4) the researcher determined other reasons that made participants unsuitable for continued participation in the study. Participants who prematurely withdrew their involvement in the study were classified as dropout cases. In the event of a participant's dropout, concerted efforts should be undertaken to establish contact with the individual to complete the assessment items and fill out the study summary page.

Grouping Method

The Geriatric Depression Scale (GDS)-30 was used to evaluate depressive symptoms in the elderly. The GDS-30 consists of 30 items, with a total score ranging from 0 and 30, where higher scores indicate more severe depression. A score of 0–-10 is considered normal, 11–-20 indicates

Table 1. Demographics and clinical characteristics of NSCLC patients (training set).

Characteristics	Non-depression group (n = 191)	Depression group (n = 59)	t/χ^2	*p*
Age (years)	63.48 ± 7.21	64.73 ± 6.89	1.176	0.241
Gender (male/female)	120 (62.83%)/71 (37.17%)	36 (61.02%)/23 (38.98%)	0.063	0.802
BMI (kg/m^2)	24.45 ± 2.81	24.87 ± 3.45	0.949	0.344
Smoking history	39 (20.42%)	11 (18.64%)	0.089	0.766
Drinking history	38 (19.90%)	11 (18.64%)	0.045	0.832
Education level				
High school or below	62 (32.46%)	20 (33.90%)	0.042	0.837
Above the high school	129 (67.54%)	39 (66.10%)		
Marital status				
Single	57 (29.84%)	19 (32.20%)		
Married	90 (47.12%)	27 (45.76%)		
Divorced	19 (9.95%)	5 (8.47%)	0.463	0.977
Widowed	15 (7.85%)	4 (6.78%)		
Other	10 (5.24%)	4 (6.78%)		
Employment status				
Unemployed	10 (5.24%)	4 (6.78%)	0.203	0.652
Employed	181 (94.76%)	55 (93.22%)		
Comorbidities				
Hypertension	56 (29.32%)	16 (27.12%)	0.106	0.744
Diabetes	53 (27.75%)	15 (25.42%)	0.123	0.726
Hyperlipidemia	44 (23.04%)	12 (20.34%)	0.189	0.664
Coronary heart disease	10 (5.24%)	4 (6.78%)	0.203	0.652
Atrial fibrillation	6 (3.14%)	3 (5.08%)	0.491	0.484
Congestive heart failure	4 (2.09%)	2 (3.39%)	0.323	0.570
Dementia	6 (3.14%)	1 (1.69%)	0.347	0.556
Epilepsy	7 (3.66%)	1 (1.69%)	0.565	0.452
Parkinson's disease	6 (3.14%)	1 (1.69%)	0.347	0.556
Chronic obstructive pulmonary disease	13 (6.81%)	5 (8.47%)	0.188	0.665
Pathology credit type				
Squamous cell carcinoma	107 (56.02%)	32 (54.24%)	0.058	0.810
Adenocarcinoma	84 (43.98%)	27 (45.76%)		
Tumor stage				
I	67 (35.08%)	19 (32.20%)	0.165	0.684
II	124 (64.92%)	40 (67.80%)		

NSCLC, non-small cell lung cancer; BMI, body mass index.

mild depression, and 21–-30 indicates moderate to severe depression. In this study, patients scoring 0–-10 were classified into the non-depression group postoperatively, while those scoring $>$ 10 were classified into the depression group postoperatively. The Cronbach's α for the GDS-30 was 0.902 [19].

Detection Indicators

General Information

The assessment primarily encompasses the following patient characteristics and clinical factors: age, gender, body mass index (BMI), smoking history, alcohol consumption history, educational status, marital status, employment status, comorbidities, pathological classification, and tumor staging.

Blood Indicators

A 3 mL sample of fasting venous blood was collected from the patient's elbow before the operation. After serum separation, the blood sample was subjected to testing for white blood cell count, platelet count, lymphocyte count, and erythrocyte sedimentation rate (ESR) using a fully automatic biochemical analyzer (BS-280, Mindray, Shenzhen, China). The serum cortisol concentration was measured using a chemiluminescent microparticle immunoassay. Additionally, red blood cell count, hemoglobin content, neutrophil count, mean red blood cell volume and monocyte count were analyzed using a fully automatic blood cell analyzer (XE2100, SYSMEX, Kobe, Japan). The NLR, LMR, and PLR were calculated based on the respective cell counts obtained from the analysis.

Table 2. Comparison of blood test between the two groups (Training set).

Parameter	Non-postoperative depression group (n = 191)	Postoperative depression group (n = 59)	t	*p*
Neutrophil/lymphocyte ratio (NLR)	3.14 ± 0.82	4.35 ± 1.23	8.715	<0.001
Lymphocyte/monocyte ratio (LMR)	5.58 ± 1.23	3.84 ± 1.58	8.849	<0.001
Platelet/lymphocyte ratio (PLR)	152.36 ± 32.46	187.46 ± 35.26	7.112	<0.001
Platelet count ($\times 10^9$/L)	250.67 ± 35.89	265.89 ± 40.12	2.768	0.006
Lymphocyte count ($\times 10^9$/L)	2.64 ± 0.64	2.35 ± 0.78	2.883	0.004
Hemoglobin (g/dL)	14.24 ± 1.68	13.66 ± 1.74	2.298	0.022
White blood cell ($\times 10^9$/L)	7.23 ± 2.13	8.12 ± 2.36	2.734	0.007
Red blood cell ($\times 10^{12}$/L)	4.79 ± 0.54	4.58 ± 0.65	2.484	0.014
Mean corpuscular volume (fL)	88.81 ± 3.58	87.51 ± 4.23	2.332	0.021
Neutrophil count ($\times 10^9$/L)	4.75 ± 1.23	5.23 ± 1.42	2.524	0.012
Monocyte count ($\times 10^9$/L)	0.73 ± 0.25	0.84 ± 0.35	2.670	0.008

Inflammatory Biomarkers

Levels of inflammatory factors in the two groups were determined by enzyme-linked immunosorbent assay (ELISA) before surgical intervention. The assessed biomarkers included tumor necrosis factor-α (TNF-α, ab181421, Abcam, Cambridge, UK), interleukin-6 (IL-6, ab178013, Abcam, Cambridge, UK), and C-reactive protein (CRP, ab260058, Abcam, Cambridge, UK), which were measured using an immunoturbidimetric assay.

Statistical Analysis

The data analysis was performed using SPSS version 29.0 statistical software (SPSS Inc, Chicago, IL, USA). Categorical data were presented in the form of [n (%)] and were subjected to the chi-square test employing the standard formula when the sample size was $\geq$40 and the theoretical frequency T was $\geq$5. When the sample size was $\geq$40, but the theoretical frequency was $1 \leq T < 5$, the chi-square test was performed using the corrected formula. In cases where the sample size was <40 or the theoretical frequency was T <1, Fisher's exact probability method was utilized for statistical analysis. The Shapiro-Wilk test was employed to assess the normality of continuous variables. For normally distributed continuous variables, the form of ($\bar{X} \pm$ s) was used, and the *t*-test with corrected variance was applied. Statistical significance was defined as two-tailed $p < 0.05$. Logistics regression analysis was used to screen the risk factors for the occurrence of depression within 90 days after surgery in NSCLC patients. The diagnostic performance of NLR, LMR, and PLR, either individually or in combination, for postoperative depression in NSCLC was evaluated using the area under the curve (AUC) of receiver operating characteristic (ROC). A joint predictive model was constructed using the multinomial distribution (multinom) and the gradient boosting machine (GBM) algorithm. Figures were generated based on the optimal thresholds.

Results

Demographics and Clinical Characteristics (Training Set)

The demographic and clinical characteristics of NSCLC patients in the training set were analyzed to investigate their association with the risk of postoperative 90-day depression (Table 1). The study cohort comprised 191 patients in the non-depression group and 59 patients in the depression group. Statistical analysis revealed no significant differences between the two groups in terms of age, gender distribution, BMI, smoking history, alcohol consumption history, education level, marital status, employment status, and comorbidities such as hypertension, diabetes, hyperlipidemia, coronary heart disease, atrial fibrillation, congestive heart failure, dementia, epilepsy, Parkinson's disease, and chronic obstructive pulmonary disease (COPD), pathology credit type, or tumor stage ($p > 0.05$). These findings suggest that the demographic and clinical characteristics of NSCLC patients in the two groups were largely comparable.

Comparison of Blood Test between the Two Groups (Training Set)

The comparison of blood parameters between the non-postoperative depression group and the postoperative depression group within the training set revealed several significant differences (Table 2). The postoperative depression group exhibited higher NLR values compared to the non-depression group (4.35 ± 1.23 vs. 3.14 ± 0.82, t = 8.715, $p < 0.001$), as well as lower LMR (3.84 ± 1.58 vs. 5.58 ± 1.23, t = 8.849, $p < 0.001$) and higher PLR (187.46 ± 35.26 vs. 152.36 ± 32.46, t = 7.112, $p < 0.001$). Additionally, the postoperative depression group exhibited higher platelet counts (265.89 ± 40.12 vs. 250.67 ± 35.89, t = 2.768, $p = 0.006$), lower lymphocyte counts (2.35 ± 0.78 vs. 2.64 ± 0.64, t = 2.883, $p = 0.004$), reduced hemoglobin levels (13.66 ± 1.74 vs. 14.24 ± 1.68, t = 2.298, $p = 0.022$), elevated white blood cell counts (8.12 ± 2.36 vs. 7.23 ± 2.13, t = 2.734, $p = 0.007$), decreased red blood cell counts

Table 3. Inflammatory biomarkers in non-postoperative depression group and postoperative depression group (Training set).

Parameter	Non-postoperative depression group (n = 191)	Postoperative depression group (n = 59)	t	*p*
CRP level (mg/L)	6.92 ± 2.18	7.89 ± 3.45	2.569	0.011
IL-6 level (pg/mL)	19.27 ± 5.89	21.45 ± 7.32	2.340	0.020
TNF-α level (pg/mL)	28.08 ± 9.45	31.46 ± 11.78	2.259	0.025
ESR level (mm/h)	18.32 ± 6.78	21.45 ± 8.32	2.931	0.004
Cortisol level (µg/dL)	21.16 ± 5.23	23.21 ± 6.78	2.444	0.015

CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; ESR, erythrocyte sedimentation rate.

(4.58 ± 0.65 vs. 4.79 ± 0.54, t = 2.484, $p = 0.014$), lower mean corpuscular volume (87.51 ± 4.23 vs. 88.81 ± 3.58, t = 2.332, $p = 0.021$), higher neutrophil count (5.23 ± 1.42 vs. 4.75 ± 1.23, t = 2.524, $p = 0.012$), and higher monocyte counts (0.84 ± 0.35 vs. 0.73 ± 0.25, t = 2.670, $p = 0.008$). These findings indicate significant differences in hematological parameters between the two groups, suggesting potential associations with the risk of postoperative 90-day depression in NSCLC patients.

Comparison of Inflammatory Biomarkers between the Two Groups (Training Set)

In the training set, a comparison of inflammatory biomarkers between the non-postoperative depression group and the postoperative depression group revealed statistically significant differences in CRP level (6.92 ± 2.18 vs. 7.89 ± 3.45, t = 2.569, $p = 0.011$), IL-6 level (19.27 ± 5.89 vs. 21.45 ± 7.32, t = 2.340, $p = 0.020$), TNF-α level (28.08 ± 9.45 vs. 31.46 ± 11.78, t = 2.259, $p = 0.025$), ESR level (18.32 ± 6.78 vs. 21.45 ± 8.32, t = 2.931, $p = 0.004$), and cortisol level (21.16 ± 5.23 vs. 23.21 ± 6.78, t = 2.444, $p = 0.015$) (Table 3). These findings suggest a potential association between inflammatory biomarkers and the risk of postoperative 90-day depression in NSCLC patients, highlighting the relevance of these biomarkers in constructing predictive models for postoperative depression risk.

Logistic Regression Analysis of the Preoperative Peripheral Blood NLR, LMR, and PLR with the Occurrence of Depression within 90 Days after Surgery in NSCLC Patients (Training Set)

The logistic regression analysis identified several preoperative peripheral blood parameters that are significantly associated with the occurrence of depression within 90 days post-surgery in NSCLC patients. Notably, higher levels of NLR, PLR, platelet count, WBC count, neutrophil count, monocyte count, CRP, IL-6, TNF-α, ESR, and cortisol were associated with an increased risk of post-surgical depression (Table 4). Conversely, higher levels of LMR, lymphocyte count, hemoglobin, RBC count, and MCV were associated with a decreased risk of post-surgical depression. These findings suggest that inflammatory markers and immune-related parameters play a crucial role in predicting post-surgical depression in NSCLC patients.

ROC (Training Set)

The predictive value of preoperative peripheral blood NLR, LMR, and PLR for the occurrence of depression within 90 days after surgery in NSCLC patients from the training set was assessed. The NLR demonstrated a sensitivity of 0.797 and specificity of 0.733, with an area under the curve (AUC) of 0.794 (Fig. 1A). In comparison, the LMR showed a sensitivity of 0.542 and a specificity of 0.937, with an AUC of 0.800 (Fig. 1B). The PLR exhibited a sensitivity of 0.712 and a specificity of 0.681, with an AUC of 0.766 (Fig. 1C). These findings suggest that NLR, LMR, and PLR have potential as predictive indicators for the occurrence of postoperative depression within 90 days, highlighting their value in constructing a multivariate predictive model for postoperative depression risk in NSCLC patients.

Finally, this study combines the predictive values of the NLR, LMR, and PLR to develop a multivariate predictive model for forecasting postoperative 90-day depression risk in NSCLC patients (Fig. 2). The AUC value of 0.931 indicates that the multivariate predictive model, based on NLR, LMR, and PLR, holds high predictive value for postoperative 90-day depression risk in NSCLC patients.

Patient Demographics and Sociodemographic Characteristics (Testing Set)

In the testing set, patient demographics and sociodemographic characteristics were compared between the non-depression group (n = 72) and the depression group (n = 28) (Table 5). The groups did not exhibit significant differences in age, gender distribution, BMI, smoking history, drinking history, education level, marital status, employment status, or comorbidities, including hypertension, diabetes, hyperlipidemia, coronary heart disease, atrial fibrillation, congestive heart failure, dementia, epilepsy, Parkinson's disease, and chronic obstructive pulmonary disease, pathology credit type, or tumor stage ($p > 0.05$). These findings indicate that the patient demographics and sociodemographic characteristics between the two groups in the testing set were largely comparable.

Table 4. Logistics regression analysis of the risk factors for the occurrence of depression within 90 days after surgery in NSCLC patients (Training set).

Parameter	SE	Wald	OR	β value	95%CI	p
Neutrophil/lymphocyte ratio (NLR)	0.211	6.367	3.832	1.343	2.604–5.978	<0.001
Lymphocyte/monocyte ratio (LMR)	0.145	–6.567	0.386	–0.952	0.285–0.505	<0.001
Platelet/lymphocyte ratio (PLR)	0.006	5.772	1.033	0.032	1.022–1.045	<0.001
Platelet count ($\times 10^9$/L)	0.004	2.688	1.011	0.011	1.003–1.020	0.007
Lymphocyte count ($\times 10^9$/L)	0.227	–2.791	0.530	–0.635	0.335–0.821	0.005
Hemoglobin (g/dL)	0.092	–2.266	0.812	–0.208	0.675–0.969	0.023
White blood cell ($\times 10^9$/L)	0.070	2.668	1.204	0.186	1.053–1.385	0.008
Red blood cell ($\times 10^{12}$/L)	0.267	–2.431	0.523	–0.648	0.306–0.876	0.015
Mean corpuscular volume (fL)	0.041	–2.293	0.910	–0.094	0.838–0.985	0.022
Neutrophil count ($\times 10^9$/L)	0.123	2.495	1.358	0.306	1.073–1.738	0.013
Monocyte count ($\times 10^9$/L)	0.553	2.593	4.197	1.434	1.444–12.754	0.010
CRP level (mg/L)	0.058	2.499	1.156	0.145	1.033–1.299	0.012
IL-6 level (pg/mL)	0.024	2.292	1.057	0.055	1.009–1.110	0.022
TNF-α level (pg/mL)	0.015	2.218	1.033	0.032	1.004–1.064	0.027
ESR level (mm/h)	0.021	2.847	1.063	0.061	1.020–1.109	0.004
Cortisol level (µg/dL)	0.027	2.385	1.066	0.064	1.012–1.124	0.017

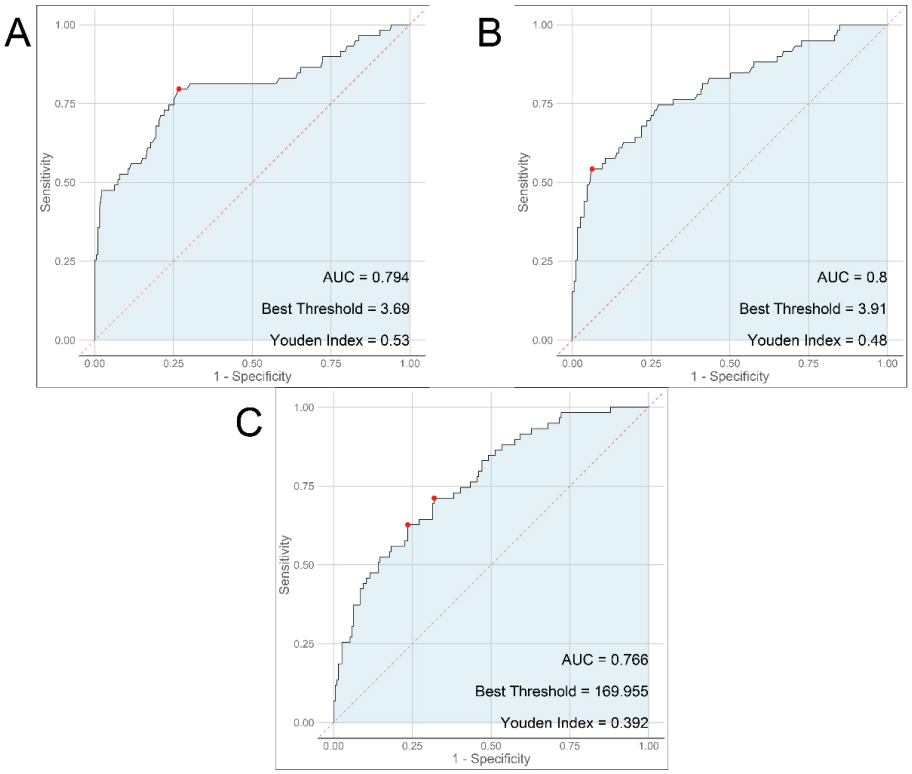

Fig. 1. Predictive value of preoperative peripheral blood NLR, LMR, and PLR for the occurrence of depression within 90 days after surgery in NSCLC patients (Training set). (A) NLR. (B) LMR. (C) PLR. AUC, area under the curve.

Comparison of Blood Test between the Two Groups (Testing Set)

The postoperative depression group exhibited a significantly higher NLR compared to the non-depression group (4.23 $\pm$ 1.24 vs. 3.13 $\pm$ 0.75, t = 5.417, $p < 0.001$) (Table 6). Similarly, the LMR was significantly lower in the postoperative depression group compared to the non-depression group (3.17 $\pm$ 1.55 vs. 4.76 $\pm$ 1.22, t = 5.412, $p < 0.001$). Additionally, the PLR was notably higher in the postoperative depression group than in the non-depression group (189.46 $\pm$ 46.58 vs. 151.48 $\pm$ 34.26, t = 4.481, $p < 0.001$). These findings suggest that consistent with the training set, the three blood parameters may be associated with the occurrence of postoperative depression.

Table 5. Patient demographics and sociodemographic characteristics (Testing set).

Characteristics	Non-depression group (n = 72)	Depression group (n = 28)	t/χ^2	*p*
Age (years)	63.65 ± 7.14	64.55 ± 7.35	0.561	0.576
Gender (male/female)	42 (58.33%)/30 (41.67%)	15 (53.57%)/13 (46.43%)	0.187	0.666
BMI (kg/m^2)	23.86 ± 2.75	23.65 ± 3.47	0.318	0.751
Smoking history	13 (18.06%)	6 (21.43%)	0.149	0.699
Drinking history	15 (20.83%)	5 (17.86%)	0.112	0.738
Education level				
High school or below	24 (33.33%)	14 (50.00%)	2.377	0.123
Above the high school	48 (66.67%)	14 (50.00%)		
Marital status				
Single	22 (30.56%)	8 (28.57%)		
Married	33 (45.83%)	12 (42.86%)		
Divorced	7 (9.72%)	3 (10.71%)	0.888	0.926
Widowed	6 (8.33%)	2 (7.14%)		
Other	4 (5.56%)	3 (10.71%)		
Employment status				
Unemployed	4 (5.56%)	3 (10.71%)	0.824	0.364
Employed	68 (94.44%)	25 (89.29%)		
Comorbidities				
Hypertension	21 (29.17%)	7 (25.00%)	0.174	0.677
Diabetes	18 (25.00%)	8 (28.57%)	0.134	0.715
Hyperlipidemia	18 (25.00%)	6 (21.43%)	0.141	0.707
Coronary heart disease	4 (5.56%)	3 (10.71%)	0.824	0.364
Atrial fibrillation	3 (4.17%)	2 (7.14%)	0.376	0.540
Congestive heart failure	2 (2.78%)	2 (7.14%)	1.000	0.317
Dementia	2 (2.78%)	3 (10.71%)	2.673	0.102
Epilepsy	1 (1.39%)	2 (7.14%)	2.294	0.130
Parkinson's disease	1 (1.39%)	2 (7.14%)	2.294	0.130
Chronic obstructive pulmonary disease	5 (6.94%)	3 (10.71%)	0.389	0.533
Pathology credit type				
Squamous cell carcinoma	41 (56.94%)	15 (53.57%)	0.093	0.760
Adenocarcinoma	31 (43.06%)	13 (46.43%)		
Tumor stage				
I	25 (34.72%)	9 (32.14%)	0.060	0.807
II	47 (65.28%)	19 (67.86%)		

BMI, body mass index.

Comparison of Inflammatory Biomarkers between the Two Groups (Testing Set)

In the testing set, a comparison of inflammatory biomarkers between the non-postoperative depression group and the postoperative depression group revealed statistically significant differences in CRP level (6.19 ± 2.14 vs. 7.52 ± 3.12, t = 2.073, $p = 0.045$), IL-6 level (19.14 ± 5.23 vs. 21.83 ± 6.03, t = 2.077, $p = 0.044$), TNF-α level (28.15 ± 9.75 vs. 32.69 ± 9.36, t = 2.152, $p = 0.036$), ESR level (18.26 ± 6.15 vs. 21.44 ± 7.24, t = 2.054, $p = 0.046$), and cortisol level (21.24 ± 5.11 vs. 23.62 ± 5.15, t = 2.085, $p = 0.042$) (Table 7). These results suggest a potential association between inflammatory biomarkers and the risk of postoperative 90-day depression in NSCLC patients, highlighting the relevance of these biomarkers in constructing predictive models for postoperative depression risk.

Logistics Regression Analysis (Testing Set)

In testing set, higher levels of NLR, PLR and CRP were associated with an increased risk of post-surgical depression (Table 8). Conversely, higher levels of LMR was associated with a decreased risk of post-surgical depression.

ROC (Testing Set)

The preoperative peripheral blood NLR, LMR, and PLR exhibited predictive value for the occurrence of depression within 90 days after surgery in the testing set of NSCLC patients. The NLR had a sensitivity of 0.750, specificity of 0.736, and an AUC of 0.771 (Fig. 3A). The LMR showed a sensitivity of 0.571, specificity of 0.958, and an AUC of 0.791 (Fig. 3B). The PLR demonstrated a sensitivity of 0.643, specificity of 0.875, and an AUC of 0.755 (Fig. 3C). These findings indicate that all three blood

Table 6. Comparison of blood tests between the two groups (Testing set).

Parameter	Non-postoperative depression group (n = 72)	Postoperative depression group (n = 28)	t	*p*
Neutrophil/lymphocyte ratio (NLR)	3.13 ± 0.75	4.23 ± 1.24	5.417	<0.001
Lymphocyte/monocyte ratio (LMR)	4.76 ± 1.22	3.17 ± 1.55	5.412	<0.001
Platelet/lymphocyte ratio (PLR)	151.48 ± 34.26	189.46 ± 46.58	4.481	<0.001

Table 7. Inflammatory biomarkers in the non-postoperative depression group and the postoperative depression group (Testing set).

Parameter	Non-postoperative depression group (n = 72)	Postoperative depression group (n = 28)	t	*p*
CRP level (mg/L)	6.19 ± 2.14	7.52 ± 3.12	2.073	0.045
IL-6 level (pg/mL)	19.14 ± 5.23	21.83 ± 6.03	2.077	0.044
TNF-α level (pg/mL)	28.15 ± 9.75	32.69 ± 9.36	2.152	0.036
ESR level (mm/h)	18.26 ± 6.15	21.44 ± 7.24	2.054	0.046
Cortisol level (μg/dL)	21.24 ± 5.11	23.62 ± 5.15	2.085	0.042

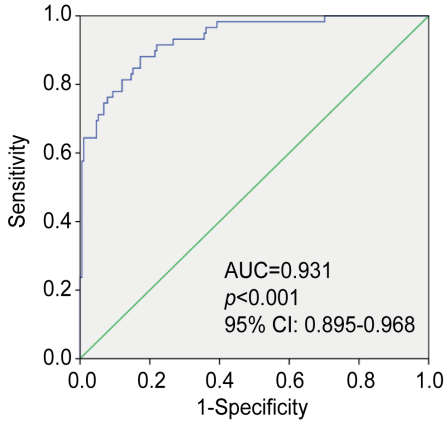

Fig. 2. Multivariate predictive model based on preoperative peripheral blood NLR, LMR, and PLR for the prediction of postoperative 90-day depression risk in NSCLC patients (Training set).

parameters have predictive value for the occurrence of postoperative depression, consistent with the results observed in the training set. This study will proceed to construct a multifactorial combined model to observe whether the predictive value in the testing set aligns with that of the training set.

Finally, this study combines the predictive value of NLR, LMR, and PLR to construct a multivariate predictive model for forecasting the risk of postoperative 90-day depression in NSCLC patients (Fig. 4). The AUC value of 0.928 indicates that the multivariate predictive model based on NLR, LMR, and PLR holds high predictive value for the risk of postoperative 90-day depression in NSCLC patients. This is consistent with the results from the training set, further strengthening the evidence of the multivariate predictive model incorporating NLR, LMR, and PLR in predicting postoperative depression in NSCLC at 90 days.

Discussion

In this prospective cohort study, we investigated the potential of preoperative peripheral blood parameters, specifically the NLR, LMR, and PLR, as predictive indicators for the risk of postoperative depression within 90 days in patients with NSCLC. Our results demonstrate significant associations between these blood parameters and the incidence of postoperative depression. Furthermore, we developed a multivariate predictive model incorporating these parameters, which shows promise for accurately predicting postoperative depression in this patient cohort.

The incidence of depression in cancer patients, particularly those undergoing surgical procedures, is a growing concern due to its significant impact on quality of life, treatment compliance, and overall clinical outcomes [20,21]. In this study, 87 out of 350 participants developed depression within 90 days after surgery, resulting in an incidence rate of 24.86%, which is relatively low compared to previous study [22]. The identification of reliable predictive biomarkers for postoperative depression is crucial for early intervention and personalized management strategies. Our study contributes to the existing body of evidence by proposing a multivariate predictive model that integrates preoperative peripheral blood parameters to assess the risk of postoperative depression in NSCLC patients.

The observed significant differences in blood parameters between the non-depression and depression groups in both the training and testing sets support the potential utility of the NLR, LMR, and PLR as predictive indicators. The elevated NLR and PLR, along with the reduced LMR in the depression group, suggest a association between systemic inflammation and the onset of postoperative depression. These findings are consistent with previous studies that have demonstrated the impact of inflammation on the pathophysiology of depression [23,24]. They emphasize the potential role of these blood parameters as markers of

Table 8. Logistics regression analysis of the risk factors for the occurrence of depression within 90 days after surgery in NSCLC patients (Testing set).

Parameter	SE	Wald	OR	β value	95%CI	p
Neutrophil/lymphocyte ratio (NLR)	0.520	12.950	6.493	1.871	2.344–17.987	<0.001
Lymphocyte/monocyte ratio (LMR)	0.346	11.315	0.313	–1.163	0.159–0.615	0.001
Platelet/lymphocyte ratio (PLR)	0.013	7.703	1.038	0.037	1.011–1.066	0.006
CRP level (mg/L)	0.182	5.526	1.534	0.428	1.074–2.193	0.019
IL-6 level (pg/mL)	0.072	2.818	1.129	0.121	0.980–1.301	0.093
TNF-α level (pg/mL)	0.044	0.151	1.017	0.017	0.933–1.109	0.697
ESR level (mm/h)	0.060	0.299	1.034	0.033	0.918–1.163	0.584
Cortisol level (µg/dL)	0.075	1.114	1.082	0.079	0.935–1.252	0.291

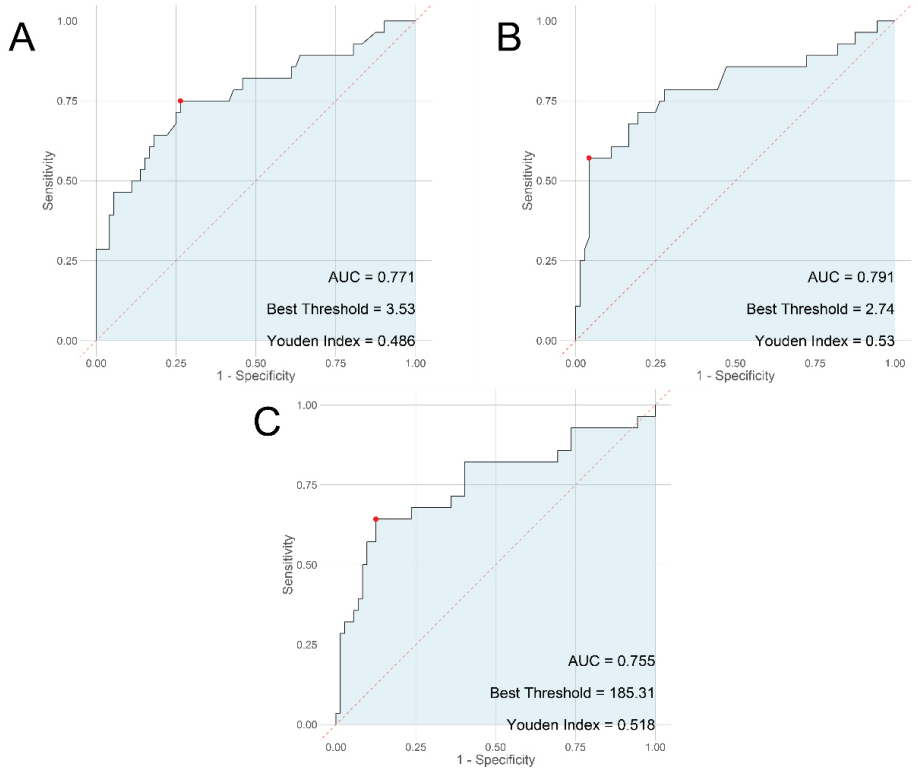

Fig. 3. Predictive value of preoperative peripheral blood NLR, LMR, and PLR for the occurrence of depression within 90 days after surgery in NSCLC patients (Testing set). (A) NLR. (B) LMR. (C) PLR.

systemic inflammatory response associated with the risk of postoperative depression in NSCLC patients.

The Logistics regression analysis further support the relationship between NLR, LMR, PLR, and the occurrence of postoperative depression, highlighting their potential as independent predictors for this outcome. The strong correlation between these hematological parameters and the occurrence of depression emphasizes their relevance in identifying patients at higher risk for postoperative depression. Moreover, the predictive value of these parameters was validated through receiver operating characteristic (ROC) curve analysis, which demonstrated their sensitivity, specificity, and area under the curve (AUC) in both the training and testing sets. The AUC values obtained for NLR, LMR, and PLR support their individual and combined predictive potential for postoperative depression risk in NSCLC patients. The development of a multivariate predictive model based on these parameters yielded high AUC values, indicating the robustness and accuracy of the model in predicting postoperative depression risk.

The observed consistency in the results between the training and testing sets strengthens the validity and generalizability of our findings. The comparable demographic and clinical characteristics between the non-depression and depression groups in both sets support the relevance of the predictive model across diverse patient populations within the context of NSCLC. The stability of the predictive model across different patient cohorts highlights its potential for clinical applicability in identifying individuals at higher risk for postoperative depression. This facilitates targeted monitoring and intervention strategies, thereby improving patient outcomes. Cohee *et al.* [25] used demographic data

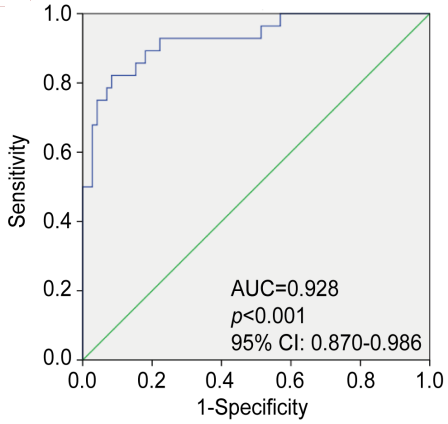

Fig. 4. Multivariate predictive model of preoperative peripheral blood NLR, LMR, and PLR for the prediction of the risk of postoperative 90-day depression in NSCLC patients (Testing set).

and clinical variables to predict improvements in depression through pain reduction. However, there are few studies on the factors influencing postoperative depression in patients with NSCLC. This study aimed to identify preoperative indicators that can forecast postoperative depression, thereby enhancing patient management. By timely prevention of postoperative depression, we seek to encourage patients to maintain effective communication with doctors and family members, sustain a positive psychological state post-surgery, and ultimately promote further rehabilitation.

The development of a multivariate predictive model for assessing postoperative depression risk based on preoperative blood parameters represents a significant advancement in the personalized management of NSCLC patients. This model integrates easily accessible blood parameters, providing a practical approach for identifying individuals at greater risk for postoperative depression. Consequently, healthcare providers can implement targeted interventions to mitigate the impact of depression on patient recovery and overall well-being. Additionally, the incorporation of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), erythrocyte sedimentation rate (ESR), and cortisol into the predictive model highlights the potential role of systemic inflammation in contributing to the risk of postoperative depression in this patient cohort. These findings are in line with existing research that associates inflammation with depression [26–28], emphasizing the need for further exploration of the underlying mechanisms and potential therapeutic targets. Moreover, our study contributes to the expanding body of literature on the intricate interplay between cancer, inflammation, and mental health. The observed association between systemic inflammatory markers, such as the NLR, LMR, PLR, and postoperative depression in NSCLC patients highlights the complex interconnections between physiological and psychological processes in patients with cancer. This finding underscores the necessity of a comprehensive, multidisciplinary approach to cancer care that addresses both physical and mental health aspects. The integration of systemic inflammatory markers into routine clinical assessments may provide valuable insights into patients' holistic well-being and guide personalized supportive care strategies.

The integration of NLR, LMR, and PLR into a predictive model for postoperative depression risk is based on the growing understanding of the complex interplay between physiological and psychological processes in cancer patients. Systemic inflammation, as indicated by these blood parameters, is increasingly acknowledged as a contributing factor not only to cancer progression but also to psychological outcomes, including depression [29,30]. Studies have demonstrated that cancer-related systemic inflammation is linked to an elevated risk of depressive symptoms [31–33], potentially due to the impact of inflammatory mediators on neurotransmitter function, neuroplasticity, and neuroendocrine pathways. Therefore, integrating these blood parameters in a predictive model for postoperative depression risk is consistent with evidence indicating a bidirectional relationship between systemic inflammation and psychological well-being in cancer patients [34–36]. Furthermore, the inclusion of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), erythrocyte sedimentation rate (ESR), and cortisol in the predictive model further substantiates the role of systemic inflammation in influencing mental health outcomes in cancer patients. These biomarkers have been implicated in the pathophysiology of depression and have been associated with depressive symptoms across various clinical populations, including cancer patients. In conclusion, the evidence supporting the development of a multivariate predictive model for postoperative 90-day depression risk in NSCLC patients, based on preoperative peripheral blood NLR, LMR, and PLR is rooted in the established associations between systemic inflammation, psychological well-being, and cancer outcomes. The integration of these blood parameters and inflammatory biomarkers into a predictive model is in line with the bidirectional relationship between systemic inflammation and mental health. This underscores the need to consider both physiological and psychological factors in cancer care. This methodology exemplifies the transition towards a multidimensional understanding of cancer and advocates for personalized strategies to address the holistic well-being of cancer patients.

Despite the promising findings, several limitations of the study should be acknowledged. First, the observational and retrospective nature of the study design introduces inherent biases, which may influence the observed associations. Prospective validation studies involving larger and more diverse patient cohorts are crucial to confirm the generalizability of the findings and assess the predictive model's performance across different clinical settings. Additionally, the study focused on a specific patient popula-

tion (NSCLC) and a specific postoperative time point of 90 days. Consequently, the generalizability of the predictive model to other cancer types and postoperative periods may be limited. Future research should explore the applicability of the model in broader oncology populations and consider longer-term outcomes. This study highlights the potential utility of NLR, LMR, and PLR as predictive markers for postoperative depression. However, the underlying mechanisms linking these blood parameters to depression risk remain unclear. Future investigations should elucidate the biological pathways through which systemic inflammation may contribute to depression in cancer patients, with a focus on identifying potential therapeutic targets. Moreover, the study did not account for potential confounding factors such as pre-existing mental health conditions, social support, and coping strategies, which may influence the risk of postoperative depression. Integrating psychosocial and behavioral factors into predictive models could enhance their accuracy and clinical utility. Finally, due to the small sample size in this study, the validation set was not used for evaluation. Consequently, only the training and test sets underwent detection analysis. This underscores the necessity for more comprehensive research in the future.

Conclusions

In conclusion, the present study provides evidence supporting the development of a multivariate predictive model for postoperative 90-day depression risk in NSCLC patients. This model is based on preoperative peripheral blood NLR, LMR, and PLR. These findings have significant implications for personalized patient care, early intervention for depression, and the integration of systemic inflammation measures into routine oncology practice. While further research and validation are warranted, the study contributes to the emerging field of precision oncology and underscores the complex interplay between cancer, inflammation, and mental health.

Availability of Data and Materials

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

Author Contributions

XW, LD and HG designed the research study. XW and CP performed the research. PZ and LM provided help and advice on the ELISA experiments. XZ analyzed the data. All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board and Ethics Committee of The First People's Hospital of Changde City (approval number: V1.0/2022.9.1), conformed to the relevant statements of the Declaration of Helsinki. All participants included in this study gave informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Li C, Lei S, Ding L, Xu Y, Wu X, Wang H, *et al*. Global burden and trends of lung cancer incidence and mortality. Chinese Medical Journal. 2023; 136: 1583–1590.

[2] Prieto M, Bobbio A, Fournel L, Icard P, Canny EH, Mansuet Lupo A, *et al*. Surgical management of resectable non-small cell lung cancer: Towards new paradigms. Bulletin du Cancer. 2020; 107: 904–911. (In French)

[3] McFarland DC, Fernbach M, Breitbart WS, Nelson C. Prognosis in metastatic lung cancer: vitamin D deficiency and depression-a cross-sectional analysis. BMJ Supportive & Palliative Care. 2022; 12: 339–346.

[4] Gallagher S, Bennett KM, Roper L. Loneliness and depression in patients with cancer during COVID-19. Journal of Psychosocial Oncology. 2021; 39: 445–451.

[5] Grassi L, Caruso R, Riba MB, Lloyd-Williams M, Kissane D, Rodin G, *et al*. Anxiety and depression in adult cancer patients: ESMO Clinical Practice Guideline. ESMO Open. 2023; 8: 101155.

[6] Szelei A, Döme P. Cancer and depression: a concise review. Orvosi Hetilap. 2020; 161: 908–916. (In Hungarian)

[7] Deng L, Chen B. Two-scale assessment of anxiety and depression in postoperative non-small cell lung cancer patients: their prevalence, risk factors, and prognostic potency. Irish Journal of Medical Science. 2023; 192: 2613–2619.

[8] Jankowska-Polańska B, Polański J, Chabowski M, Rosińczuk J, Mazur G. Influence of Coping Strategy on Perception of Anxiety and Depression in Patients with Non-small Cell Lung Cancer. Advances in Experimental Medicine and Biology. 2020; 1251: 57–70.

[9] Song M, Zhang Q, Song C, Liu T, Zhang X, Ruan G, *et al*. The advanced lung cancer inflammation index is the optimal inflammatory biomarker of overall survival in patients with lung cancer. Journal of Cachexia, Sarcopenia and Muscle. 2022; 13: 2504–2514.

[10] McFarland DC, Breitbart W, Miller AH, Nelson C. Depression and Inflammation in Patients with Lung Cancer: A Comparative Analysis of Acute Phase Reactant Inflammatory Markers. Psychosomatics. 2020; 61: 527–537.

[11] McFarland DC, Jutagir DR, Miller AH, Breitbart W, Nelson C, Rosenfeld B. Tumor Mutation Burden and Depression in Lung Cancer: Association with Inflammation. Journal of the National Comprehensive Cancer Network: JNCCN. 2020; 18: 434–442.

[12] Beurel E, Toups M, Nemeroff CB. The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron. 2020; 107: 234–256.

[13] Kofod J, Elfving B, Nielsen EH, Mors O, Köhler-Forsberg O. Depression and inflammation: Correlation between changes in inflammatory markers with antidepressant response and long-term prognosis. European Neuropsychopharmacology. 2022; 54: 116–125.

[14] Halaris A. Inflammation and depression but where does the inflammation come from? Current Opinion in Psychiatry. 2019; 32: 422–428.

[15] Brown RB. Stress, inflammation, depression, and dementia associated with phosphate toxicity. Molecular Biology Reports. 2020; 47: 9921–9929.

[16] Harsanyi S, Kupcova I, Danisovic L, Klein M. Selected Biomarkers of Depression: What Are the Effects of Cytokines and Inflammation? International Journal of Molecular Sciences. 2022; 24: 578.

[17] Velasco A, Lengvenyte A, Rodriguez-Revuelta J, Jimenez-Treviño L, Courtet P, Garcia-Portilla MP, *et al*. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review. European Psychiatry. 2023; 1–25.

[18] Mazza MG, Tringali AGM, Rossetti A, Botti RE, Clerici M. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. General Hospital Psychiatry. 2019; 58: 7–12.

[19] Cialdella P, Guillaud-Bataille JM, Gausset MF, Terra JL, Gerin P, Palliard E, *et al*. Etude sur l'unidimensionnalité de l'échelle de dépression gériatrique de Yesavage et Brink. Comparaison entre méthodes classiques et modèle de Rasch [Study of the uni-dimensionality of the Yesavage-Brinck geriatric depression scale. Comparison between classical methods and Rasch's model]. Encephale. 1992; 18: 537–544.

[20] Götze H, Friedrich M, Taubenheim S, Dietz A, Lordick F, Mehnert A. Depression and anxiety in long-term survivors 5 and 10 years after cancer diagnosis. Supportive Care in Cancer. 2020; 28: 211–220.

[21] Marinovic DA, Hunter RL. Examining the interrelationships between mindfulness-based interventions, depression, inflammation, and cancer survival. CA: A Cancer Journal for Clinicians. 2022; 72: 490–502.

[22] Huang X, Zhang TZ, Li GH, Liu L, Xu GQ. Prevalence and correlation of anxiety and depression on the prognosis of postoperative non-small-cell lung cancer patients in North China. Medicine. 2020; 99: e19087.

[23] Wei Y, Feng J, Ma J, Chen D, Chen J. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in patients with affective disorders. Journal of Affective Disorders. 2022; 309: 221–228.

[24] Zhu X, Li R, Zhu Y, Zhou J, Han X, Tong Y, *et al*. Neutrophil/lymphocyte, platelet/lymphocyte, monocyte/lymphocyte ratios and systemic immune-inflammation index in patients with depression. Bratislavske Lekarske Listy. 2023; 124: 471–474.

[25] Cohee AA, Kroenke K, Vachon E, Wu J, Tu W, Johns SA. Predictors of depression outcomes in adults with cancer: A 12 month longitudinal study. Journal of Psychosomatic Research. 2020; 136: 110169.

[26] Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: A meta-analysis. Journal of Affective Disorders. 2020; 277: 940–948.

[27] Medina-Rodriguez EM, Cruz AA, De Abreu JC, Beurel E. Stress, inflammation, microbiome and depression. Pharmacology, Biochemistry, and Behavior. 2023; 227-228: 173561.

[28] Liu M, Li Y, Liu X. Serum tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-17 relate to anxiety and depression risks to some extent in non-small cell lung cancer survivor. The Clinical Respiratory Journal. 2022; 16: 105–115.

[29] Sipahi H, Mat AF, Ozhan Y, Aydin A. The Interrelation between Oxidative Stress, Depression and Inflammation through the Kynurenine Pathway. Current Topics in Medicinal Chemistry. 2023; 23: 415–425.

[30] Milaneschi Y, Kappelmann N, Ye Z, Lamers F, Moser S, Jones PB, *et al*. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. Molecular Psychiatry. 2021; 26: 7393–7402.

[31] Bhatt S, Devadoss T, Jha NK, Baidya M, Gupta G, Chellappan DK, *et al*. Targeting inflammation: a potential approach for the treatment of depression. Metabolic Brain Disease. 2023; 38: 45–59.

[32] Liu CH, Zhang GZ, Li B, Li M, Woelfer M, Walter M, *et al*. Role of inflammation in depression relapse. Journal of Neuroinflammation. 2019; 16: 90.

[33] Kronsten VT, Tranah TH, Pariante C, Shawcross DL. Gut-derived systemic inflammation as a driver of depression in chronic liver disease. Journal of Hepatology. 2022; 76: 665–680.

[34] Slavich GM, Sacher J. Stress, sex hormones, inflammation, and major depressive disorder: Extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. Psychopharmacology. 2019; 236: 3063–3079.

[35] Suneson K, Lindahl J, Chamli Hårsmar S, Söderberg G, Lindqvist D. Inflammatory Depression-Mechanisms and Non-Pharmacological Interventions. International Journal of Molecular Sciences. 2021; 22: 1640.

[36] Leonard BE, Wegener G. Inflammation, insulin resistance and neuroprogression in depression. Acta Neuropsychiatrica. 2020; 32: 1–9.