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ABSTRACT

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INFLAMMATION INDEXES AS PREDICTORS OF RECURRENCE IN PATIENTS WITH SURGICALLY RESECTED NON-SMALL CELL LUNG CANCER

Introduction. Prediction of lung cancer recurrence is one of the most urgent problems of modern oncology. Scientists are trying to find independent predictors that will help intensify, personalize the patient's treatment, and prevent the disease relapse on time.

The study aimed to find indicators of inflammation that could be independent predictors of disease recurrence in patients with surgically resected non-small cell lung cancer.

Materials and methods. The study was conducted retrospectively. The study group included 104 patients with non-small cell lung cancer who received surgical treatment and adjuvant chemotherapy or chemoradiotherapy from 2014 to 2018 at the Sumy Regional Clinical Oncology Dispensary. Based on the results of the blood count tests, the inflammation indices were calculated before chemotherapy or chemoradiotherapy and one month after their completion. Systemic inflammatory response index (SIRI), systemic inflammatory index (SII), neutrophil/lymphocyte ratio (NLR), platelets/lymphocytes ratio (PLR), lymphocyte/monocyte ratio (LMR), monocyte/lymphocyte ratio (MLR) were calculated. Using ROC analysis, cut-off points were found. Cox regression was used to find independent predictors of lung cancer recurrence.

Results. During the observation period, relapse of the disease was recorded in 42 (40.4%) patients. The average recurrence-free survival was 56.3 months, range of 4–84.0 months (95% CI = 46.866–65.683). Before chemo- or chemoradiation therapy, the cut-off points for NLR1, PLR1, MLR1, LMR1, SII1, and SIRI1 were 1.80, 126.35, 0.22, 4.80, 521.22 and 0.96, respectively. Cut-off points for NLR2, PLR2, MLR2, LMR2, SII2, and SIRI2 at stage one month after completing courses of chemotherapy or chemoradiotherapy were 1.33, 153.80, 0.26, 3.98, 450.10 and 0.82 respectively. According to ROC analysis, only PLR1, SII1, LMR1, and LMR2 indices are reliable and can be used in further Cox regression analysis. Univariant Cox regression showed that LMR1 and SII1 were significantly associated with disease recurrence. Multivariate Cox regression identified SII1 as the only independent predictor of disease recurrence.

Conclusions. Among numerous inflammation indices as an independent predictor for disease recurrence in non-small cell lung cancer patients who received surgical treatment and chemotherapy or chemoradiotherapy, only systemic inflammation index (SII1) at the stage before chemotherapy or chemoradiotherapy can be used. Indicators above 521.22 could be a predictor of high-risk recurrence of lung cancer.

Keywords: non-small cell lung cancer, chemotherapy, chemoradiotherapy, recurrence, index.

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РЕЗЮМЕ

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ЗАПАЛЬНІ ІНДЕКСИ ЯК ПРЕДИКТОРИ РЕЦИДИВУ У РАДИКАЛЬНО ПРООПЕРОВАНИХ ПАЦІЄНТІВ З НЕДРІБНОКЛІТИННИМ РАКОМ ЛЕГЕНЬ

Вступ. Прогнозування рецидиву раку легень є однією з найактуальніших проблем сучасної онкології. Вчені намагаються знайти незалежні предиктори, які допоможуть вчасно інтенсифікувати, персоніфікувати лікування пацієнта та попередити появу рецидиву захворювання.

Метою дослідження було знайти показники запалення, які можуть бути незалежними предикторами рецидиву захворювання у пацієнтів із хірургічно видаленим недрібноклітинним раком легені.

Матеріали та методи. Дослідження проводилося ретроспективно. До складу досліджуваної групи увійшло 104 пацієнти з недрібнокітинним раком легень, які отримали хірургічне лікування та ад'ювантну хіміо- або хіміопроменеву терапію у період з 2014 по 2018 роки у Сумському обласному клінічному онкологічному диспансері. На підставі результатів клінічного аналізу крові були пораховані індекси запалення на етапі перед хіміо- або хіміопроменевою терапією та через місяць після їх завершення. Зокрема, підраховано індекс системної запальної відповіді (SIRI), індекс системного запалення (SII), співвідношення нейтрофіли/лімфоцити (NLR), співвідношення тромбоцити/лімфоцити (PLR), співвідношення лімфоцити/моноцити (LMR), співвідношення моноцити/лімфоцити (MLR). За допомогою ROC аналізу встановлено точки відсічення. Регресійний аналіз Кокса використанно для встановлення незалежних предикторів рецидиву раку легень.

Результати. Протягом усього періоду спостереження рецидив захворювання було зафіксовано у 42 (40,4%) пацієнтів. Середнє безрецидивне виживання становило 56,3 місяця, діапазон 4–84,0 місяця (95% ДІ = 46,866–65,683). Точками відсічення для NLR1, PLR1, MLR1, LMR1, SII1 та SIRI1 на етапі до проведення хіміо- або хіміопроменевої терапії визнано 1,80, 126,35, 0,22, 4,80, 521,22 та 0.96 відповідно. Точками відсічення для NLR2, PLR2, MLR2, LMR2, SII2 та SIRI2 на етапі через один місяць після завершення курсів хіміо- або хіміопроменевої терапії визнано 1,33, 153,80, 0,26, 3,98, 450,10 та 0,82 відповідно. Згідно

ROC аналізу лише індекси PLR1, SII1, LMR1 та LMR2 є достовірними та можуть використовуватися у подальшому регресійному аналізі Кокса. Однофакторний регресійний аналіз Кокса показав, що LMR1 і SII1 були значно пов'язані з рецидивом захворювання. Багатофакторний регресійний аналіз Кокса визначив SII1 як єдиний незалежний предиктор рецидиву захворювання.

Висновки. Серед численних індексів запалення незалежним предиктором рецидиву недрібноклітинного раку легень у пацієнтів, що отримали хірургічне лікування та хіміо- або хіміопроменеву терапію є лише індекс системного запалення (SII1) на етапі до хіміо- або хіміопроменевої терапії. Показники вище 521,22 є свідченням високого ризику рецидиву раку легень.

Ключові слова: недрібноклітинний рак легені, хіміотерапія, хіміопроменева терапія, рецидив, індекс.

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INTRODUCTION / ВСТУП

Lung cancer is one of the most common reasons for cancer-related death. Despite early detection and timely treatment, recurrence of the disease occurred in more than 30% of cases [1]. To predict the possibility of recurrence, different factors are examined. The most common factors influencing disease recurrence are stage, smoking status, histological type, and size [4]. New factors are investigating now. Inflammation indexes are one of them. There are numerous inflammatory indices, and despite that, novels are investigated. The Neutrophil/lymphocyte ratio (NLR) is the most widely used and common index. For the last few years, many indices have been additionally investigated. Among them are the Systemic inflammatory response index (SIRI), Systemic inflammation index (SII), Lymphocyte/monocyte ratio (LMR), and others. Using inflammatory indices is cost-effective and can be used everywhere because they are based on blood count. That is why their usage is very promising due to numerous advantages.

The aim of the study was to find inflammation indexes that can be independent predictors of disease recurrence in a patient with surgically resected non-small cell lung cancer.

Materials and methods

Study design. The study was retrospective and included 104 patients. All patients received definitive treatment according to the standards of the NCCN (National Comprehensive Cancer Network)**.** Patients were treated in the Sumy Regional Clinical Oncology Center (Ukraine) from 2014 to 2018. Exclusion criteria were neoadjuvant chemotherapy and/or radiation therapy, positive resection margins, the appearance of a new malignancy, and complications after surgery. The study group also excluded patients with the IA stage and some with the IB stage who did not require or had contraindications to adjuvant chemotherapy. For the investigation, complete blood count tests were used. The tests were performed before and one month after the completion of all courses of chemotherapy.

Inflammation indexes. Based on blood count tests that were performed before (1) and one month after (2) chemotherapy, main inflammation indexes were calculated. They include systemic inflammatory response index (SIRI), Systemic inflammation index (SII), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), monocyte-lymphocyte ratio (MLR).

The systemic inflammatory response index (SIRI) was calculated as a ratio:

$$SIRI = \frac{N \times M}{L},$$

The systemic inflammation index (SII) was calculated as a ratio:

$$SII = \frac{P \times N}{L},$$

The neutrophil/lymphocyte ratio (NLR) was calculated as a ratio:

$$NLR = \frac{N}{L},$$

Platelet/lymphocyte ratio (PLR) was calculated as a ratio:

$$PLR = \frac{P}{L},$$

The lymphocyte/monocyte ratio (LMR) was calculated as a ratio:

$$LMR = \frac{L}{M},$$

Monocyte-lymphocyte ratio (MLR) was calculated as a ratio:

$$MLR = \frac{M}{L},$$

where M – monocytes in peripheral blood (cells/L), N – neutrophils in peripheral blood (cells/L), L – lymphocytes in peripheral blood (cells/L), and P – platelets in peripheral blood (cells/L) [2].

Follow-up of patients after surgical treatment and adjuvant chemotherapy

Patients were monitored according to the standards of NCCN. The first computed tomography was performed one month after surgery. This examination was repeated every three months during the first three years, then – every six months for the next two years. After five years after the surgery, CT was performed once a year. MRI of the brain, ultrasound of the neck, abdominal cavity, pelvis, and bone scans was performed as needed in case of suspicion of recurrence of the disease.

The Ethics Committee. The study was performed retrospectively. We adhered to the Declaration of Helsinki and received the approval of the Local Ethics Commission of the Sumy Regional Clinical Oncology Center.

Statistical analysis. Cox regression was used to create the model for the survival of patients with lung cancer. The main advantage of this model is that it allows working with categorical and censored data.

The receiver-operating characteristic (ROC) analysis was used to find cut-off points. The method aims to build a graphical tool for displaying the accuracy of a diagnostic test. In this method, the measures of accuracy are sensitivity (true positive rate), specificity (true negative rate), and area under the curve (AUC). ROC curve is a plot of sensitivity on the *y-axis* against (1−specificity) on the *x-axis* for varying values of the threshold t. The 45° diagonal line connecting (0,0) to (1,1) is the ROC curve corresponding to random chance. The ROC curve for the gold standard is the line connecting (0,0) to (0,1) and (0,1) to (1,1) [3].

The standard data model was created in Excel, and the analytical model – was in the software environment IBM SPSS Statistics 27. All calculations were also made in the software environment SPSS. The risk factors were significant when the two-sided P value was less than 0.05.

Results. During the follow-up period, recurrence of the disease occurred in 42 (40.4%) patients, and 38 (90.5%) of them died. Another 4 (9.5%) people died of other causes. The recurrence-free survival rate was 58.8%. The median recurrence-free survival was 56.3 months, range of 4–84.0 months (95% CI = 46.866–65.683).

At first, we investigated inflammatory indexes before adjuvant chemotherapy/chemoradiation therapy. ROC –analysis showed that inflammatory indexes before chemotherapy/chemoradiation therapy were more sensitive and could be used as diagnostic tests (Fig. 1).

As shown in Figure 1, the area under the curves (AUC) of NLR1, PLR1, MLR1, LMR1, SII1, and SIRI1 were 0.469, 0.596, 0.478, 0.523, 0.527, and 0.477, respectively, and the optimal cut-off values were 1.80, 126.35, 0,22, 4.80, 521.22, and 0.96, respectively.

After this, we evaluated the impact of inflammatory markers on disease recurrence one month after the completion of courses of adjuvant chemotherapy/chemoradiation therapy (Fig. 2).

As shown in Figure 2, the area under the curves (AUC) of NLR2, PLR2, MLR2, LMR2, SII2, and SIRI2 were 0.394, 0.503, 0.4748, 0.528, 0.446, and 0.417, respectively, and the optimal cut-off values were 1.33, 153.80, 0.26, 3.98, 450.10 and 0.82, respectively.

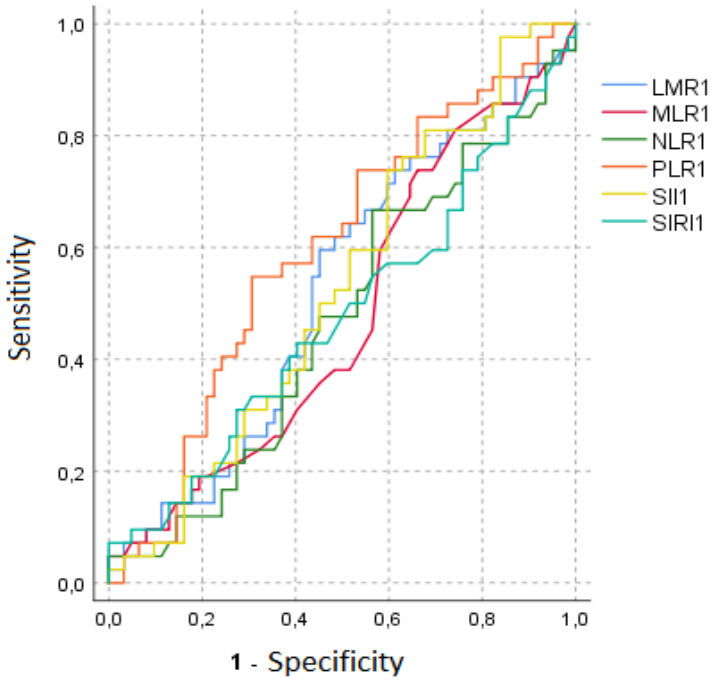

Figure 1 – ROC curve analysis for optimal cut-off value of inflammation indexes before chemotherapy/chemoradiation therapy for PFS

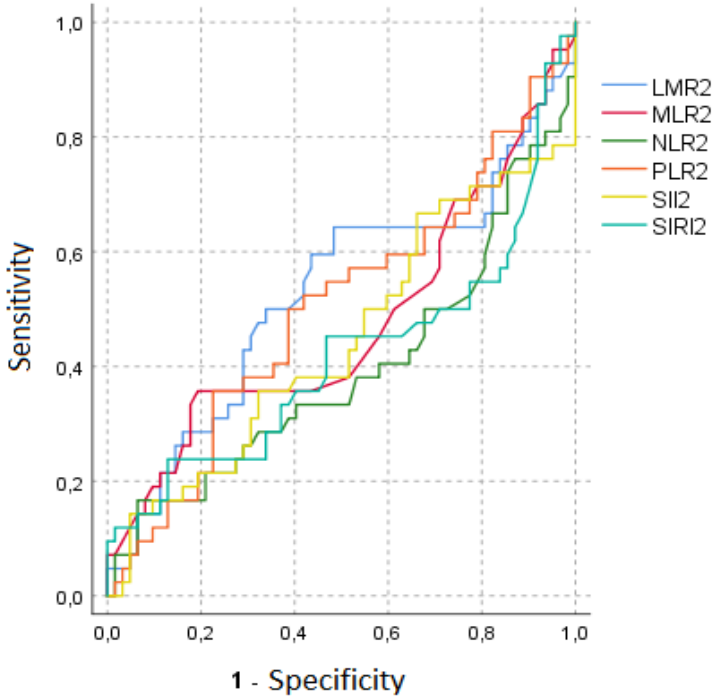

Figure 2 – ROC curve analysis for optimal cut-off value of inflammation indexes after chemotherapy/chemoradiation therapy for PFS

Due to data obtained from curve analysis, PLR1, SII1, LMR1and LMR2 had appropriate accuracy. Our previous study detected category T, histological differentiation, and smoking status as independent predictors of disease recurrence in patients with surgically resected non-small-cell lung cancer [4]. The Cox regression was used to identify independent predictors of recurrence in the current study (Table 1).

Table 1 – Univariate and multivariable analyses of inflammation indices associated with recurrence-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
LMR_1	0.71 (0.38–1.33)	0.0285	1.68 (0.92–4.42)	0.45
LMR_2	1.04 (0.57–1.91)	0.899		
PLR_1	1.19 (0.64–2.24)	0.577		
SII_1	0.97(0.53–1.79)	0.00930	0.84 (0.54–1.76)	0.006

According to Univariate Cox regression analyses, LMR1, and SII1 were significantly associated with disease recurrence. Multivariate Cox regression analyses identified SII1 as the only independent predictor of disease recurrence.

Discussion. Investigation of inflammation indexes is currently relevant. Their influence on disease progression is widely studied for different types of tumors: lung, breast, and digestive system neoplasms [5], stomach cancer [6], and small-cell lung cancer [7]. Investigation of the influence of inflammatory indexes on disease recurrence in patients with lung cancer is now widely made.

There are many different studies on disease recurrence and inflammatory indexes that show different results. In other studies, different indexes were correlated with poor prognosis. In some of them, such a correlation was not found.

We studied the influence on disease recurrence of different inflammatory indexes. However, other scientists also investigated overall survival. Thus, Yang et al. conducted a meta-analysis that examined the effect of SII and other inflammatory markers on Overall Survival (OS), Progression-Free Survival (PFS), Disease-Free Survival (DFS), and Relapse-Free Survival (RFS). Elevation of SII was associated with poor prognosis for most cancers, including small and non-small cell lung cancer. According to the study, patients with stomach cancer were an exception. An index score higher than the cut-off point indicates a poor OS, but the cut-off point is not the same for different cancers and must be determined individually for each [8]. It was also detected that inflammatory indices correlated with prognosis [9]. For lung cancer patients increase in inflammatory indicators correlated with a poor prognosis [10] and increased mortality risk [11]. Our investigation showed that inflammatory indices could independently predict disease recurrence.

Over the last five years, numerous investigations have been made on lung cancer and inflammatory indices. Due to the results of our study, the only independent predictor of disease recurrence was SII calculated before chemotherapy/ chemoradiation therapy. Patients with an increase of the SII of more than 521 had more chances for disease recurrence. Thus, Huang et al. investigated the influence of inflammatory indices, particularly SII, on survival in patients with non-small cell lung cancer. As a result, it was determined that patients with a high index level had worse survival than patients with a lower index. It was also determined that patients with the II-III stage of the disease had a higher SII index [12]. Obtained data also correlated with the investigation of Qi [13] and Tong [14]. Abravan et al. also described NLR (per 1 unit: hazard ratio [HR]: 1.04, $p < 0.05$) and SII (per 100×10^9/L: HR: 1.01, $p < 0.05$) as independent factors of OS in early-stage and locally advanced NSCLC and SCLC patients treated with RT [15]. Unfortunately, in our investigation, NLR neither before nor after treatment did not show even appropriate sensitivity. That is why we cannot use NLR as a marker that correlates with poor prognosis and disease recurrence.

Another group of researchers found that in patients with non-small cell lung cancer who received chemoradiation treatment, an increase in SII was determined to indicate a reduction in OS. Interestingly, the Δ SII indicator shows the index's growth level during treatment and has the most significant predictive value. Cut off point for Δ SII was detected as 43. If the Δ SII was less than 43, OS and FSP were more outstanding. Also, Δ SII score was found to be an independent predictor for OS and FSP [16]. Delikgoz et al. showed that optimal cut-off values for NLR, PLR, dNLR and SII were 3.07, 166, 2.02, and 817, respectively. Blood samples were taken before therapy. Low NLR, PLR, dNLR, and SII were significant prognostic factors for PFS. Low NLR, low dNLR, and low SII groups had better radiosensitivity than high NLR, high dNLR, and high SII groups (P =

0.001, P = 0.001, and P = 0.012) [17]. In our investigation, the cut-off point for SII was 521, which differs from the analysis of Delikgoz. As mentioned earlier, indices cut-off points should be indicated individually for each case and location.

In the case of ALK mutation in patients with non-small cell lung cancer who received appropriate first-line targeted therapy, the duration of PFS was determined to be associated with baseline PLR, and SII, as well as the SII, score three weeks after initiation of therapy. Indexes were measured before and three weeks after drug administration [18]. Ju et al. found that lower SII was associated with prolonged survival in patients with different EGFR mutant lung adenocarcinomas. SII before treatment was a powerful indicator for the PFS and OS of patients who received the first-generation EGFR-TKI [19]. Also was detected that patients with signs of pre-therapeutic inflammation (elevated NLR, SII, IL-6, IL-8) showed a significantly lower response to immune checkpoint inhibitor (ICI) treatment and reduced PFS [20]. In our study, we did not consider mutation status because of the low cover level in the population.

It was also found that inflammatory markers influenced major pathological responses in patients with stage I-IIIB non-small cell lung cancer. Thus, the on-treatment NLR, dNLR, PLR, and SII levels were significantly lower in the patients with major pathologic response (MPR) versus non-MPR. On-treatment SII remained an independent predictor of MPR in multivariate logistic regression analysis [21].

On the other hand, only preoperative MLR levels (p = 0.0269) were identified as an independent predictor of shorter RFS in patients with surgically resected IA NSCLC. Preoperative high MLR levels were significantly associated with sex, smoking status, and postoperative recurrence (p < 0.0001, p = 0.0307, and p = 0.0146, respectively), and preoperative high SII levels were significantly correlated with postoperative recurrence (p = 0.0458). NLR and PLR were not associated with any related factors [22]. In comparison to our investigation, neither MLR or NLR or PLR can be used as independent predictors.

Coutu et al. found that in patients who underwent neoadjuvant radiation in addition to 3 cycles of chemotherapy (carboplatin and paclitaxel) followed by surgical resection (86.4% lobectomy and 13.6% pneumonectomy) with mediastinal lymph node dissection, a low SII (< 1,260) at diagnosis was independently associated with an improved OS (hazard ratio [HR]: 0.448, p = 0.004), DFS (HR: 0.366, p < 0.001), and FFR (HR: 0.325, p = 0.002) [23]. Łochowski et al. investigated the influence on prognosis in patients treated due to IA-IIIA stage NSCLC. Blood samples were collected before surgery. It was found that PLR and SII index are independent prognostic factors [24]. A low SII was associated with female gender, never smoking status, adenocarcinoma histology, higher pathological TNM stage, and low level of serum C-reactive protein. Patients with low SII had a significantly better 5-year overall survival (83.61% vs. 60.39%, p < 0.001). Multivariate analysis showed SII as an independent predictive indicator for cancer-specific survival (p = 0.007) [25]. On the other hand, higher NLR (≥ 2.606), SIRI (≥ 0.705), SII (≥ 580.671), and category T4 were significantly associated with worse cancer-specific survival (CSS) and DFS. Higher NLR, SII, and SIRI pretreatment were associated with worse survival outcomes [26].

In our study, we did not investigate advanced stages of lung cancer, but as we can see, results in advanced stages were similar to those in early stages. In patients with advanced NSCLC, lymphocyte-to-C-reactive protein ratio and SIRI were identified as independent prognosticators for both PFS and OS (P < 0.001, P < 0.001; P = 0.002, P < 0.001, respectively) [27]. Another group of investigators found that increased levels of SII were predictors of worth prognosis in patients with advanced NSCLC. SII was also an independent predictor of PFS and OS [28]. Data correlated with Berardis' team [29]. Gao et al. found that high SII was significantly associated with advanced T stage and positive lymph node metastasis. Multivariate analysis identified SII as an independent predictor of OS [30].

Zhang et al. found out that patients with NSCLC and brain metastasis treated with Stereotactic Radiotherapy had better median PFS in patients with low SII (11.5 vs. nine months). An SII > 480 was significantly associated with worse OS (HR: 2.196; 95% CI 1.259-3.832; P = 0.006) and PFS (HR: 2.471; 95% CI 1.488-4.104; P < 0.001) according to univariate analysis. In multivariate analysis, only SII (HR: 2.224; 95% CI 1.298-3.810; P = 0.004) was an independent prognostic predictor of PFS. Blood samples were taken a week prior to stereotactic radiotherapy [31]. Banna et al. showed that the number of metastatic sites ≥ 3 (p < 0.001 and p = 0.002), squamous histology (p = 0.033 and p = 0.013), and SII ≥ 1444 (p = 0.031 and

p = 0.009, respectively) were associated with both worse OS and PFS [32]. However, none of the prognostic factors and inflammatory indices (NLR, PLR, SII, LMR) were statistically significant in terms of overall survival in both univariate and multivariate analysis [33].

CONCLUSIONS / ВИСНОВКИ

Among numerous inflammation indices as an independent predictor for disease recurrence in non-small cell lung cancer patients who received surgical treatment and chemotherapy or chemoradiotherapy, only systemic inflammation index (SII1) at the stage before chemotherapy or chemotherapy can be used. Indicators above 521.22 could be predictors of high-risk recurrence of lung cancer.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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