ORIGINAL ARTICLE

THE ROLE OF SERUM URIC ACID AND URIC ACID TO ALBUMIN RATIO FOR PREDICTING OF LYMPH NODE METASTASIS IN LUNG CANCER TREATED SURGICALLY BY VATS

Muhammet Sayan*[1], Merve Satir Turk[1], Dilvin Ozkan[1], Aykut Kankoc[1], İsmail Tombul[1], Ali Celik[1]

[1] Department of Thoracic Surgery, Gazi University, 06560, Ankara, Turkey

* **Corresponding author:** drsayann@gmail.com

Abstract

Objectives: *In recent years, a correlation between prognosis of various cancers and inflammation has been emphasized in many studies. Here, we have investigated whether preoperative serum uric acid levels, albumin levels, and uric acid to albumin ratio predict lymph node metastasis in non-small cell lung cancer treated surgically by VATS.*

Methods: *The medical records of patients who underwent VATS lobectomy/segmentectomy for non-small cell lung cancer between January 2015 and December 2020, were reviewed retrospectively. Groups with and without lymph node metastasis and high and low groups with high and low uric acid to albumin ratio were created. Pearson chi-square test was used to investigate whether any significant correlation between the groups existed.*

Results: *A total of 115 patients were included in the study. Lymph node metastasis in N1 and N2 stations was detected in 11 and 18 patients, respectively. There was a statistically significant correlation between lymph node metastasis and high uric acid levels (p=0.008, OR: 3.2) and high uric acid to albumin ratio (p=0.03, OR: 2.6)..*

Conclusions: *Preoperative serum uric acid and uric acid to albumin ratio can predict the lymph node metastasis in non-small cell lung cancer treated surgically by video assisted thoracic surgery.*

Keywords: *Non-small cell lung cancer, VATS, lobectomy, segmentectomy, uric acid.*

INTRODUCTION

Although new prognostic indicators such as tumor burden, genetic and molecular pathways have been discovered, tumor stage is still very important in determining the prognosis of lung cancer. Determinants of tumor stage are tumor diameter, regional lymph node metastasis and distant metastasis. Lymph node metastasis which is not detected in clinical staging but diagnosed in pathological staging is called occult lymph node metastasis (OLM) or occult nodal diseases, and patients with OLM have a worse prognosis than those with node negative. Despite all invasive clinical staging efforts, OLM incidence has been reported as about 10% in NSCLC[1]. In recent years, studies investigating whether there is a correlation between inflammation and NSCLC have increased in the literature[2-3]. Uric acid which is a purine metabolite was formerly known as an antioxidant protecting against the carcinogenesis[4]. However, more recent studies have shown that uric acid has a complex role in cancer biology, as high serum uric acid level(SUA) has been associated with early cancer deaths[5-6]. Although some studies have claimed that cancer risk was increased by high SUA, others have reported SUA was elevated by death of cancer cells as a cell degradation product. So, a definitive cause and effect relationship has not been established between SUA and risk of cancer and its prognosis[6-8]. A Mendelian randomization study collecting some genomic studies reported that there was no correlation between uric acid and risk of developing various cancers including NSCLC. The results of that study have demonstrated that uric acid is an indicator of tumor aggressiveness rather than being an etiologic factor for

cancer[9]. Another poor indicator reported for cancer prognosis is hypoalbuminemia. Albumin is a major component of serum protein and it is used as a parameter reflecting nutritional status and cancer aggressiveness. Serum albumin levels have been used in many studies as a part of some prognostic scores such as Glaskow Prognostic Score which reflects prognosis of lung cancer[10-12]. The aim of our study was to investigate the role of SUA, albumin and uric acid to albumin ratio (UAR) for predicting OLM in patient with NSCLC treated by lobectomy or segmentectomy by Video-assisted thoracic surgery (VATS).

MATERIALS AND METHODS

Ethical approval for this study was obtained from Gazi University Ethics Committee (approval number: 2021-756). Informed consent was not obtained because there is no need for this in retrospective archive studies according to the laws of our country.

Patient Selection

Medical records of patients who underwent VATS lobectomy/segmentectomy with mediastinal lymph node dissection or sampling between January 2015 and December 2020, were retrospectively reviewed. Inclusion criteria were as follows; patients operated by VATS for primary NSCLC and those who underwent mediastinal lymph node dissection or sampling. Patients who underwent wedge resection, lobectomy or segmentectomy for metastatic lung lesions, had any diseases or medications which could affect the inflammation and SUA (acute or chronic renal failure, morbid obesity, gout, connective tissue diseases, active or chronic liver diseases, induction chemotherapy, alcoholism, active infection, and use of corticosteroid, anti-inflammatory agent etc.) and those whose follow-up or preoperative blood test records could not be obtained, were not included the study. Additionally, we did not include in the study patients who underwent thoracotomy to ensure homogeneity, because we aimed to ensure that the lymph node dissection effectiveness was not different.

Preoperative assessment

Patients were evaluated according to guidelines in the preoperative period. Preoperative assessment included routinely blood test (Complete Blood Count, renal and liver function tests, protein, albumin, uric acid, electrolytes, coagulation parameters, cross match, C-Reactive protein, and hepatitis markers), pulmonary function tests, carbon monoxide diffusion test, electrocardiogram, thorax computed tomography, PET-CT, and cranial MRI. In addition, necessary cardiopulmonary exercise tests and consultations were performed when needed. Patients with enlarged mediastinal LAP, those with large and centrally located tumor were referred to Endobronchial ultrasound guided transbronchial needle aspiration biopsy (EBUS-TBNA) or mediastinoscopy. While patients who had metastatic mediastinal lymph nodes were directed to neoadjuvant or curative chemotherapy, pulmonary resection was planned for those without mediastinal lymph node metastasis.

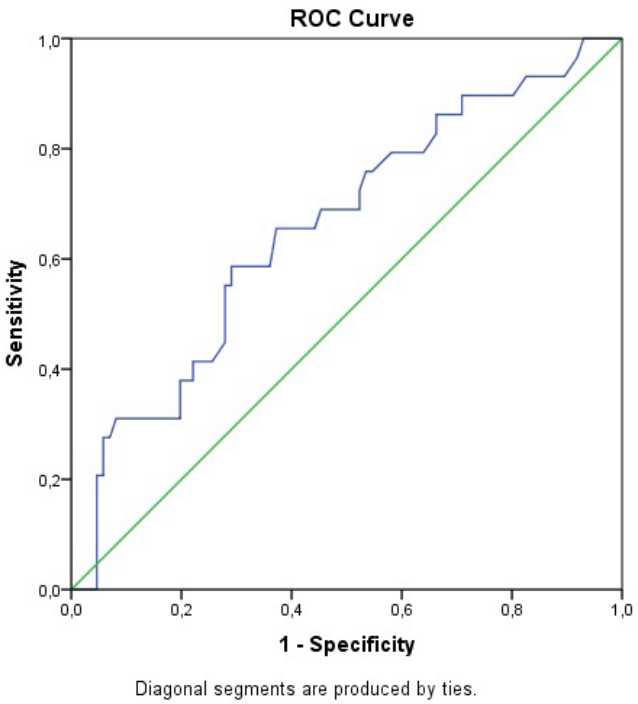

Figure 1 *ROC curve of serum uric acid level according to lymph node invasion status (p=0.01, area under the curved: 75%, cut-off value: 5.97).*

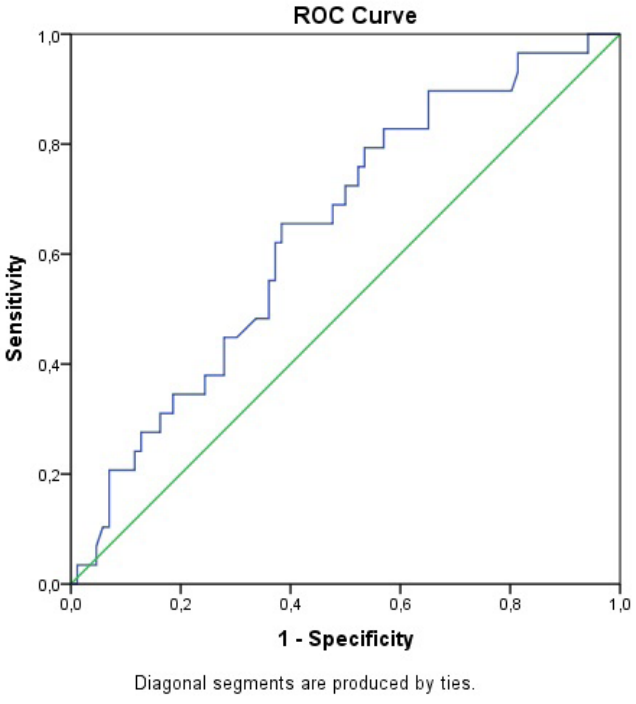

Figure 2 *ROC curve of serum uric acid to albumin ratio according to lymph node invasion status (p=0.02, area under the curved: 70.3%, cut-off value: 1.28.10-3).*

Blood Samples

The result of blood tests obtained before hospitalization and during the preparation for surgery was used for this study to prevent the effect of metabolic/emotional stress and medication on the inflammatory parameters. Blood samples were taken from peripheral veins.

For complete blood count (CBC); sufficient blood sample was taken into vacuum tube with EDTA. The analysis was performed using the Beckman Coulter UniCel® machine.

For uric acid and albumin tests, enough blood samples were taken into vacuum tubes with gel and clot activator. The biochemical analysis was performed by spectrophotometric method using the Beckman® AU5800 auto-analyzer.

Statistical analysis

All statistical analyzes were performed using the SPSS 20 (IBM, Armonk, NY, US) software. Distribution of numeric variables was evaluated by histogram and Kolmogrov-Smirnov test. The mean ± standard deviation (SD) was used for normal distributions and median value with range (minimum-maximum) was used for skewed distributions. Cut-off values, significance and area under curved (AUC) were determined for some variables by Receiver Operating Characteristics (ROC) analysis method. According to cut-off values, high and low groups were created. In addition, according to hilar and/or mediastinal lymph node invasion, positive and negative groups were formed. Significance between the groups and Odds Ratio (OR) were investigated by Chi-square test. We have investigated whether there was a significant correlation between some inflammatory parameters which were obtained by preoperative CBC tests and lymph node invasion status using ROC analysis. These inflammatory parameters were as follows; platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet distribution width (PDW), red cell distribution width (RDW). In addition, we investigated whether there was any correlation between tumor FDG avidity and lymph node metastasis status. Another research topic was the correlation between mediastinal and tumoral 18f-FDG uptake and level of inflammatory parameters. Analyzes were performed with 95% confidence interval (CI), 2-sided p value was calculated a p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of one hundred fifteen patients who fulfilled the inclusion criteria were included in the study. There were 39 (34%) females and 76 (66%) males. Median age was 64 (range: 40-85) years old. Median tumor diameter was 2 (range 0.6-7) cm. General characteristics of patients are given in Table 1. The lymph nodes that were routinely dissected by operation side were as follows; in right-sided resections; paratracheal (#2 and/or #4), subcarinal (#7), pulmonary ligament (#9), hilar (#10) and interlobar (#11) stations, in left-sided resections; paraaortic (#6), aorticopulmonary (#5), subcarinal (#7), hilar (#10), and interlobar (#11) stations. However, right and left sided paraesophageal (#8) and left paratracheal (#4) lymph nodes were not routinely dissected. We have not detected any significant correlation between OLM and some inflammatory parameters including PLR, NLR, LMR, PDW and RDW by ROC analysis ($p>0.05$, Table 2). However, that correlation was statistically significant for uric acid ($p=0.01$) and uric acid to albumin ratio (UAR, $p=0.02$, Table 2). Cut-off values with sensitivity and specificity for SUA and UAR were 5.97 mg/dL and $1.28.10^{-3}$ respectively. Groups with and without lymph node invasion were compared to those with high/low SUA and UAR using Pearson Chi-square test. As a result, a significant correlation was found between lymph node metastasis and serum uric acid ($p = 0.008$, OR: 3.2) and UAR ($p = 0.03$, OR: 2.6, Table 3). The median SUV of tumors on PET-CT was 4,0 (Range 0-13,1). There was no marked mediastinal involvement of 18f-FDG since most patients were in the early clinical stage. There was no significant correlation between SUV and inflammatory parameters. Additionally, we did not detect significant correlation SUV of tumor or mediastinal lymph nodes and pathological lymph node metastasis status.

DISCUSSION

Our study demonstrated that preoperative high SUA and high UAR were useful for predicting OLM in lung cancers treated by VATS resection. While there are many survival studies in the published data regarding various cancer types and serum uric acid levels, those including prediction of lymph node metastasis are scarce. Ustuner MA et al.performed a survival study in patients with colorectal cancer[13]. They calculated cut-off value for SUA as 5.3 mg/dL and reported that hyperuricemia is a poor prognostic factor for colorectal carcinoma. Another study reported that preoperative high SUA levels are related to poor prognosis in patients with esophagus squamous cell carcinoma[14]. Articles investigating SUA and lung cancer prognosis are very few in the literature. Yang et al. investigated whether there was a correlation between lung cancer and uric acid to lymphocyte ratio (ULR)[15]. They claimed that both lymphopenia and hyperuricemia was a poor prognostic factor for overall survival (OS) and they determined cut–off value for ULR by ROC analysis as 3.83 and reported that OS was worse in high ULR group. We have not performed a survival analysis because the surgery dates of the patients were generally close to the end-date of study date and the number of patients who completed 5-years was not sufficient. Instead, we evaluated lymph node metastasis status, which is an indirect determinant of survival, and we could not find any significant correlation between lymph node metastasis status and ULR by ROC analysis in our study. Although a study demonstrated pre-treatment high SUA level correlated with low survival and high risk of cranial metastasis in patients with NSCLC treated with first line chemotherapy, the underlying mechanism could not be fully explained[16]. Similarly, our study indicated that preoperative hyperuricemia was a predictor of OLM which is an indirect indicator of cancer aggressivity. Related studies showed that elevated SUA level triggered inflammatory stress

Table 1 **Characteristics of patients, n=115**

Variables		n	%
Age (median-range)	64 (40-85) years		
Tumor Diameter (median-range)	2 (0.6-7) cm		
Gender	Female	39	34
	Male	76	66
Histopathology			
	Adeno CA	72	62,6
	Adeno-squamous cell CA	1	0,9
	Carcinoid tumor	6	5,2
	ACC	2	1,7
	Squamous cell CA	24	20,9
	PPS	2	1,7
	LCNE	4	3,5
	Small Cell CA+ adeno CA	1	0,9
	Sarcomatoid CA	3	2,6
N Status			
	N0	86	74,8
	N1	11	9,6
	N2	18	15,7
Type of Surgery			
	Segmentectomy	10	8,7
	LUL	26	22,6
	BLS	1	0,9
	LLL	19	16,5
	RLL	22	19,1
	RML	10	8,7
	RUL	25	21,7
	RUSL	2	1,7
Tumor Stage (8th TNM)			
	I-A1	13	11,3
	I-A2	38	33,0
	I-A3	10	8,7
	I-B	18	15,7
	II-A	4	3,5
	II-B	13	11,3
	III-A	19	16,5
VPI			
	Yes	17	14,8
	Nil	98	85,2
Uric Acid level (mg/dL)			
	High	51	44,3
	Low	64	55,7
Uric acid to Albumin Ratio (10-3)			
	High	64	55,7
	Low	51	44,3

Abbreviations: ACC: Adenoid Cystic Carcinoma, BLS: Bilobectomy Superior, CA: carcinoma, LCNE: Large Cell Neuroendocrine Tumor, LLL: Left Lower Lobectomy, LUL: Left Upper Lobectomy, PPS: Primary Pulmonary Sarcoma, RLL: Right Lower Lobectomy, RML: Right Middle Lobectomy, RUL: Right Upper Lobectomy, RUSL: Right Upper Sleeve Lobectomy.

and intracellular pro-oxidative activity. Pro-oxidant environments accelerate tumor growth by stimulating signal pathways which regulate cell proliferation and apoptosis. Additionally, the anti-carcinogenic effect of allopurinol which is a xanthine oxidase inhibitor is an indirect predictor of carcinogenic features of uric acid[17-18]. Studies also reported that elevated SUA level increases cancer related mortality. The carcinogenic and fatal effect of uric acid was explained as SUA level causes chronic inflammation by reactive oxygen species[19].

Another poor prognostic factor for lung cancer is hypoalbuminemia. The albumin has been investigated itself or as a part of some prognostic scores, in survival studies including patients with lung cancer treated by both surgical and non-surgically. Fiala et al. reported the hypoalbuminemia was a poor prognostic for survival in patients with advanced stage NSCLC treated with tyrosine kinase inhibitor[20]. Similarly, Li X et al. detected that high albumin to globulin ratio was a good indicator of both OS and disease free survival[21]. Our study was performed in patients with early clinical cancer stage and marked hypoalbuminemia was not an expected status. Thus, while hypoalbuminemia did not correlate significantly with predicting OLM in itself, the correlation was significant for UAR by ROC analysis. The rate of OLM was significantly high in groups with high UAR in our study. We have not found any study investigating whether there is a correlation between OLM and UAR in the English literature. To our knowledge, this study is the first to demonstrate that a high SUA and UAR level is a predictor of OLM in patients with NSCLC treated surgically.

Table 2 **Results of Receiver Operating Characteristic (ROC) Analysis and related values according to some parameters**

Parameters	Median Value (range)	Cut-Off Value	Sensitivity (%)	Specifity (%)	Standart Error	*p* value	AUC (%)
Uric acid	5,60 mg/dL, (2.9-9.89)	5.97	74	69	,059	0.01	75
UAR	1.34 (0.6-2.9)	1.28.10-3	72	61	,057	0.02	70.3
Albumin	4.3 g/dL (3.17-4.90)	-	59	57	,057	0.08	60.7
ULR	2.74 (0.4-13.7)	-	50	58	,064	0.2	57.5
PLR	129.8 (18.2-461.3)	-	55	52	,069	0.4	54.2
NLR	2.31 (0.14-10.6)	-	46	55	,065	0.8	51.1
RDW	13.5 (11.9-21.5)	-	48	55	,067	0.8	51.5
PDW	11.5 (8.5-17.8)	-	58	55	,064	0.4	54.5
LMR	2.58 (0.46-8.17)	-	58	60	,065	0.6	52.7

Abbreviations: AUC: Area Under theCurved, LMR: LymphocytetoMonocyteRatio, NLR: NeutrophiltoLymphocyteRatio, PLR: Platelet toLymphocyteRatio, PDW: Platelet Distribution Width, RDW: Red Cell Distribution Width, , UAR: UricAcid to AlbuminRatio, , ULR: UricAcidtoLymphocyteRatio.

Table 3 **Results of Pearson chi-square test and odds ratios between the groups, n=115**

		Lymph node invasion positive	Lymph node invasion negative			
High Uric Acid		n=19	n=32			
	EC	12.9	38.1			
				0.008	3.2	1.3-7.7
Low Uric Acid		n=10	n=54			
	EC	16.1	47.9			
High UAR						
	EC	n=21	n=43			
Low UAR		16.1	47.9			
				0.03	2.6	1.0-6.5
	EC	n=8	n=43			
		12.9	38.1			

Abbreviations: OR: Odds Ratio, EC: Expected Count, CI: Confidence Interval, UAR: Uric Acid to Albumin Ratio

Limitations of our study were as follows, this is a retrospective and single-centered study, and it included a small number of patients.In addition, surgery date of most patients included in the study was close to the study end date, so we did not perform survival analyses to avoid false results. Another consequence of the small number of patients is that the study included a wide histopathological spectrum. For this reason, multicenter studies with a large number of patients and a single histopathology are needed. Another limitation, occult N2 rate of our study was higher than literature. The possible reason for this was that invasive mediastinal staging such as mediastinoscopy was not performed on all patients, especially those with small, peripheral tumors. We performed invasive mediastinal staging for patients with mediastinal involvement in PET-CT, those with centrally located and large tumors by EBUS, EUS, mediastinoscopy and rarely mediastinotomy and VATS. Although in some guidelines, mediastinoscopy is recommended in high-risk patients even if there is no tumor in EBUS we did not perform mediastinoscopy in all risky patients.

CONCLUSION

Results of our study can give an idea to physicians that preoperative SUA and UAR can be used as a marker for predicting OLM in patients with NSCLC treated surgically by VATS. Despite clinical staging efforts, care should be taken for OLM in patients whose lymph nodes are not found to have tumors and whose parameters are high.

REFERENCES

1. Bille A, Woo KM, Ahmad U, Rizk NP, Jones DR. Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. Eur J Cardiothorac Surg 2017;51:674-679.
2. Łochowski M, Chałubińska-Fendler J, Zawadzka IK, Łochowska B, Rębowski M, et al. The prognostic significance of preoperative platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in patients operated for non-small cell lung cancer. Cancer Management and Research2021;13:7795-7802.
3. Łochowski M, Łochowska B, Chałubińska-Fendler J, Zawadzka I, Rębowski M, Kozak J. Prognostic factors determining survival of patients operated for non-small cell lung cancer with consideration given to morphological parameters of blood. Cancer Manag Res 2021;13:479-487.
4. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981;78:6858-6862.
5. Petersson B, Trell E. Raised serum urate concentration as risk factor for premature mortality in middle aged men: relation to death from cancer. Br Med J (Clin Res Ed) 1983;287:7-9.
6. Fini MA, Elias A, Johnson RJ, Wright RM. Contribution of uric acid to cancer risk, recurrence, and mortality. Clin Transl Med 2012;1:16.
7. Boffetta P, Nordenvall C, Nyrén O, Ye W. A prospective study of gout and cancer. Eur J Cancer Prev 2009;18:127-132.
8. Huang CF, Huang JJ, Mi NN, Lin YY, He QS, et al. Associations between serum uric acid and hepatobiliary-pancreatic cancer: A cohort study. World J Gastroenterol 2020;26:7061-7075.
9. Jiang M, Ren L, Chen S, Li G. Serum uric acid levels and risk of eight site-specific cancers: a Mendelian randomization study. Front Genet 2021;12:608311.
10. Pan M, Zhao Y, He J, Wu H, Pan Y, et al. Prognostic value of the glasgow prognostic score on overall survival in patients with advanced non-small cell lung cancer. J Cancer 2021;12:2395-2402.
11. Takamori S, Takada K, Shimokawa M, Matsubara T, Fujishita T, et al. Clinical utility of pretreatment Glasgow prognostic score in non-small-cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer 2021;152:27-33.
12. Vaz Souza R, Bassi M, Mantovani S, Poggi C, Diso D, et al. Comparison of preoperative scores predicting outcome in elderly undergoing lung malignancies resection. J Thorac Dis 2020;12:7083-7088.
13. Ustuner MA, Dogan L. Relationship of preoperative serum uric acid level with survival in colorectal cancer. J Coll Physicians Surg Pak 2020;30:717-721.
14. Chen YF, Li Q, Chen DT, Pan JH, Chen YH, et al. Prognostic value of pre-operative serum uric acid levels in esophageal squamous cell carcinoma patients who undergo R0 esophagectomy. Cancer Biomark 2016;17:89-96.
15. Yang Z, Li S, Zhao L, Lv W, Ju J, et al. Serum uric acid to lymphocyte ratio: A novel prognostic biomarker for surgically resected early-stage lung cancer. A propensity score matching analysis. Clin Chim Acta 2020;503:35-44.
16. Tanriverdi O, Cokmert S, Oktay E, Pilanci KN, Menekse S, et al. Prognostic significance of the baseline serum uric acid level in non-small cell lung cancer patients treated with first-line chemotherapy: a study of the Turkish Descriptive Oncological Researches Group. Med Oncol 2014;31:217.
17. Shi Y. Caught red-handed: uric acid is an agent of inflammation. J Clin Invest. 2010;120:1809-1811.
18. Mi S, Gong L, Sui Z. Friend or foe? An unrecognized role of uric acid in cancer development and the potential anticancer effects of uric acid-lowering drugs. Journal of Cancer 2020;11:5236-5244.
19. Yan S, Zhang P, Xu W, Liu Y, Wang B, Jiang T. et al. Serum uric acid increases risk of cancer incidence and mortality: a systematic review and meta-analysis. Mediators Inflamm2015;2015:764250.
20. Fiala O, Pesek M, Finek J, Racek J, Minarik M, et al. Serum albumin is a strong predictor of survival in patients with advanced-stage non-small cell lung cancer treated with erlotinib. Neoplasma 2016;63:471-476.
21. Li X, Qin S, Sun X, Liu D, Zhang B, et al. Prognostic significance of albumin-globulin score in patients with operable non-small-cell lung cancer. Ann Surg Oncol 2018;25:3647-3659.