ORIGINAL ARTICLE

Impacts of Preoperative Smoking and Smoking Cessation Time on Preoperative Peripheral Blood Inflammatory Indexes and Postoperative Hospitalization Outcome in Male Patients with Lung Cancer and Surgery Treatment

Longming Xu^{1#}, Shuiping Dai^{2#}, Yunxia Zuo^{1*}

¹Department of Anesthesiology, West China Hospital,
Sichuan University, Chengdu 610041, China

²Department of Respiratory Medicine, West China Hospital,
Sichuan University, Chengdu 610041, China

Key words: smoking; smoking cessation; lung cancer; surgical treatment; inflammatory factors; postoperative outcomes

Objectives To investigate the effects of preoperative smoking and smoking cessation time on preoperative peripheral blood inflammatory indexes and postoperative hospitalization outcomes in male patients with lung cancer and surgery therapy.

Methods We retrospectively enrolled 637 male patients who underwent curative-intent lung cancer resection between January 2014 and December 2016. Patients were classified as the current smokers, the never smokers, and the ex-smokers based on their smoking history, and the ex-smokers were allocated into five subgroups according to their smoking cessation times (CeT): $CeT \leq 6$ weeks, $6weeks < CeT \leq 1year$, $1year < CeT \leq 5years$, $5years < CeT \leq 10years$, $CeT > 10years$. The preoperative peripheral blood white blood cells (WBCs), albumin, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), intraoperative blood loss, 30-day mortality, in-hospital days, hospitalization costs, intensive care unit (ICU), admission days and placement time of closed thoracic drainage tube were compared among different groups.

Results There were significant differences in WBC ($F = 5.275$, $P < 0.001$) and albumin ($F = 2.470$, $P < 0.05$) among patients of current smokers, ex-smokers with different smoking cessation time, and never-smokers. The

Received July 8, 2019; accepted March 29, 2020; published online June 16, 2020.

[#]These authors contributed equally to this work.

*Corresponding author E-mail: zuoyxhxa@163.com.

Fund supported by the National Key R&D Program of China (No. 2018YFC2001800).

blood WBC count in current smokers ($7.7 \times 10^9/L$) was significantly higher than that in ex-smokers ($7.0 \times 10^9/L$) and never-smokers ($5.9 \times 10^9/L$) ($t = -2.145$, $P < 0.05$; $t = -6.073$, $P < 0.01$, respectively). The level of peripheral blood albumin in current smokers (41.1 g/L) was lower than that in ex-smokers (42.1 g/L) and never-smokers (43.2 g/L) ($t = 2.323$, $P < 0.05$; $t = 3.995$, $P < 0.01$, respectively). The level of peripheral blood NLR in current smokers (3.7) was higher than that in ex-smokers (3.1) and never smokers (2.8) ($t = -1.836$, $P < 0.05$; $t = -2.889$, $P < 0.01$, respectively). There was no significant difference in WBC, albumin and NLR among five subgroups of different smoking cessation time. No significant difference was observed in intraoperative blood loss, 30-day mortality, hospitalization costs, hospital stay, ICU stay and placement time of closed thoracic drainage tube among groups either.

Conclusion Smoking increases the preoperative inflammatory indexes in peripheral blood of lung cancer patients. Smoking cessation has beneficial effect on reducing levels of these inflammatory indexes, which may be not impacted by the time length of smoking cessation. Therefore, lung cancer patients should be encouraged to quit smoking at any time.

SMOKING is a risk factor for intraoperative and postoperative complications. It increases the incidence of in-hospital morbidity and mortality,^[1] and increases surgical blood loss as well.^[2] During lung surgeries, compared to never-smokers, current smokers had higher frequencies of postoperative pulmonary complications (PPC) and intensive therapy unit admission.^[3] Of 156 000 people who die of lung cancer each year, those current smoker patients also had higher hospital costs compared to the never-smoker patients (relative cost, 1.04; 95% CI, 1.00-1.07).^[4] Smokers are more likely to develop pneumonia, accidental endotracheal intubation, and therefore require mechanical ventilation. They are also more likely to have cardiac arrest, myocardial infarction, or stroke. Therefore, smoking cessation is very important to improve the prognosis of patients with lung cancer. Studies have shown that the time of smoking cessation for at least 6 weeks before operation, rather than immediately before surgery, might be more beneficial.^[5] Some studies have suggested that in order to reduce incidence of PPC, smoking cessation should be at least 4 weeks before operation.^[6] The most appropriate time of smoking cessation before surgery for lung cancer patients has not been identified.

In 1863, Rudolf Virchow, a German medical scientist, proposed a link between inflammation and tumors. Smoking is associated with some peripheral serum markers,^[7] including white blood cells (WBC),^[8] C reactive protein (CRP),^[9] and albumin.^[10] Studies have shown that cigarettes contain addictive nicotine, which activates neutrophils in body and plays

an important role in inflammation.^[9] Some studies have found that the serum levels of WBC, CRP and albumin after smoking cessation were similar to that of never-smokers,^[10, 11] elevated neutrophil to lymphocyte ratio (NLR), elevated platelet to lymphocyte ratio (PLR), and low albumin level were predictors of poor overall survival in patients with lung cancer.^[12-17] According to our knowledge, few studies has focused on the correlation of smoking cessation time with preoperative serum WBC, PLR, albumin and NLR in patients with lung cancer. The current retrospective cohort study was carried out to further explore and analyze the effects of preoperative smoking and smoking cessation time on peripheral blood WBC, PLR, NLR, albumin, 30-day mortality, in-hospital days, hospitalization costs, ICU admission days and placement time of closed thoracic drainage tube in male patients with lung cancer.

PATIENTS AND METHODS

Patients selection

This study was approved by the institutional committee of biomedical ethics. Male patients of lung cancer who underwent curative-intent lung cancer resection between January 2014 and December 2016 in West China Hospital Sichuan University were retrospectively collected in this study. All patients were re-classified by the 8th edition International Association for the Study of Lung Cancer (IASLC) classification system. The including criteria were: 1) newly diagnosed lung cancer patients; 2) underwent curative surgeries, including open thoracotomy or video-assisted thoracoscopic

surgery (VATS); 3) male patients and aged 18 years or older. Patients were excluded if they had any of the following situations: 1) preoperative treatment for lung cancer (e.g., preoperative radiotherapy, chemotherapy, or targeted therapy); 2) pulmonary infection or any other systems infection before operation; 3) smoking history was not clearly described in the medical record.

Information collection and patients grouping

We retrospectively collected patients' information from the Hospital Information System (HIS) and the Laboratory Information system (LIS). The clinical information included age, sex, body mass index (BMI), history of smoking, smoking cessation time, histopathology, IASLC stage; the preoperative peripheral blood inflammatory indexes included WBC, albumin, platelet, neutrophil, and lymphocyte counts; the post-operative hospitalization outcome indexes included 30-day mortality, surgical blood loss, placement time of closed thoracic drainage tube, days of intensive care unit (ICU) admission, in-hospital days, and death of any cause. We also recorded the hospitalization expense of each patient. Patients were assigned into groups based on smoking history. Never-smoker was defined as smoking fewer than 100 cigarettes during lifetime; current smokers were those who still smoked at admission; ex-smokers were those who smoked more than 100 cigarettes during lifetime but did not smoke at admission. Ex-smokers were allocated as following sub-groups according to the smoking cessation time (CeT): $CeT \leq 6w$, $6w < CeT \leq 1y$, $1y < CeT \leq 5y$, $5y < CeT \leq 10y$, and $CeT > 10y$.

Statistical analysis

Quantitative data were described by means and standard deviation (SD) or median, while qualitative data were expressed by adoption rate. We compared the variables of blood inflammation indexes and post operation hospitalization outcomes among groups of smoker, ex-smoker and never smokers. Pearson's chi-square test or Fisher's exact test was used for comparing categorical variables, and analysis of variance (ANOVA) or t ' test for comparing quantitative variables among multiple groups and between any two groups. The difference of baseline clinical characteristics among multiple groups was also examined. All analyses were conducted using SPSS (Version 19.0, IBM). $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients

Totally 637 eligible male patients diagnosed with lung cancer and treated with surgery were included in this study, with age from 18 to 83 years old, and the mean age of 59.5 ± 9.6 years old. The mean BMI was 23.0 ± 2.9 kg/m². Of all patients, 27.8% ($n=177$) were current smokers, 58.4% ($n=372$) were ex-smokers, and 13.8% ($n=88$) were never-smokers. The most common operation performed was lobectomy (92.8%), followed by segmentectomy/wedge (6.6%), and the least common was sleeve resection (0.6%). A significant difference was observed in age among different smoking groups ($F=6.814$, $P < 0.001$), of which patients with smoking cessation ≥ 10 years were the oldest (mean, 64.84 ± 10.7 years old). The percentage of lung cancers in stage I was 18.8% ($n=120$), in stage II was 30.8% ($n=196$), in stage III was 45.1% ($n=287$), and in stage IV was 5.3% ($n=34$), with no significant difference among the groups ($\chi^2=26.079$ $P=0.098$). No significant difference in BMI among the groups was found ($F=1.049$, $P=0.537$). The baseline characteristics of all included patients were presented in **Table 1**.

Preoperative inflammatory indexes in blood

Significant differences in WBC count ($F=4.28$, $P < 0.001$) and albumin ($F=7.040$, $P < 0.01$) were found among the current smokers, ex-smokers and never-smokers. When combining the current smokers and ex-smokers together, the mean values of smokers were significantly different compared to the never-smoker patients in preoperative blood WBC ($7.2 \times 10^9/L$ vs. $5.9 \times 10^9/L$, $t=4.28$, $P < 0.001$) and albumin (41.7 g/L vs. 43.2 g/L, $t=-2.88$, $P < 0.01$). Both ex-smokers and never-smokers had significantly lower WBC levels ($t=-2.415$, $P < 0.05$; $t=-6.073$, $P < 0.01$) and higher albumin ($t=2.323$, $P < 0.05$; $t=3.995$, $P < 0.01$) than the current smokers (**Table 2**).

The NLR were significantly different among the current smokers, ex-smokers and never smokers ($F=4.727$, $P < 0.01$), and the current smokers had significantly higher NLR than both never smokers and ex-smokers (both $P < 0.05$). No significant difference was found in PLR among the current smokers, ex-smokers and never smokers and between any two of the groups (**Table 2**).

In ex-smokers with different smoking cessation time ($CeT \leq 6w$, $6w < CeT \leq 1y$, $1y < CeT \leq 5y$,

Table 1. Baseline characteristics of patients with lung cancer in different groups of smoking status and smoking cessation time

Characteristics	Current smoker (n=177)	Ex-smoker (n=372)					Never-smoker (n=88)	F/ χ^2	P
		CeT≤6w (n=90)	6w<CeT≤1y (n=107)	1y<CeT≤5y (n=86)	5y<CeT≤10y (n=34)	CeT>10y (n=55)			
Age [years, mean(SD)]	57.9 (8.0)	59.9 (8.6)	58.1 (8.5)	60.7 (8.4)	63.7 (7.2)	64.8 (10.7)	57.7 (13.3)	4.525	0.000
BMI [kg/m ² , mean (SD)]	22.7 (3.3)	22.9 (2.9)	22.9 (2.9)	23.1 (2.9)	24.1 (2.3)	23.2 (2.7)	23.5 (2.6)	1.049	0.537
8th edition IASLC Classification [n (%)]								26.079	0.098
Stage I	32 (18.1)	18 (20.0)	14 (13.1)	18 (20.9)	6 (17.6)	6 (17.6)	19 (21.6)		
Stage II	46 (26.0)	32 (35.6)	41 (38.3)	31 (36)	12 (35.3)	9 (16.4)	25 (28.4)		
Stage III	93 (52.5)	36 (40.0)	42 (39.3)	33 (38.4)	13 (38.2)	32 (58.2)	38 (43.2)		
Stage IV	6 (3.4)	4 (4.4)	10 (9.3)	4 (4.7)	3 (8.8)	1 (1.8)	6 (6.8)		
Surgery procedures [n (%)]								9.888	0.626
Lobectomy	165 (93.2)	85 (94.4)	102 (95.3)	79 (91.9)	31 (91.2)	47 (85.5)	82 (93.2)		
Segmentectomy/wedge	110 (5.6)	4 (4.4)	5 (4.7)	7 (8.1)	3 (8.8)	7 (12.7)	6 (6.8)		
Sleeve	1 (1.1)	1 (1.1)	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)		

CeT, cessation time; BMI, body mass index; IASLC, International Association for the Study of Lung Cancer; SD, standard deviation.

5y<CeT≤10y, and CeT>10y), the preoperative WBC levels and albumin levels were not statistically different (all $P>0.05$) by ANOVA. Similarly, no significant differences were found in NLR and PLR among these patient groups (**Table 3**).

Postoperative hospitalization outcomes

The 30-day mortality of current smokers, ex-smokers and never smokers was 2.8%, 3.0% and 1.1% respectively (Fisher's exact test, $P>0.05$); when combining the current and ex-smokers together, although the ever smoking patients has a 30-day mortality of 2.9%, which was much higher than that of never-smokers, there was no statistical difference (Correction for continuity, $\chi^2=0.0.365$, $P=0.294$). No differences were found in hospitalization costs, in-hospital days, ICU admission days, surgery blood loss, and placement time of closed thoracic drainage tube among current smokers, ex-smokers and never-smokers (**Table 2**).

In subgroup patients with different smoking cessation time, the above measures were not significantly different either (**Table 3**), although the intra operative blood loss of never-smoking patient was the least (153.8 ml), and the current smokers patients had the highest hospitalization costs (mean, 71 072.9 Yuan), while the never smoking group had the lowest hospitalization costs (mean, 60 546.8 Yuan), with as much as 10 526.1 yuan difference between the two groups.

The hospitalization time, ICU stay time and placement time of closed thoracic drainage tube were the longest in current smokers patients (median, 11 days, 3 days and 6 days, respectively), and the least in never smoking group (median, 9 days, 2 days and 4 days, respectively), but all differences were not statistically significant.

DISCUSSION

Lung cancer is the leading cause of cancer-related death in the world.^[18] Researches have found that quitting smoking is highly beneficial in reducing lung cancer risk for smokers regardless of their CHRNA5rs16969968 genetic risk status.^[19] However, quitting smoking for better life is still an important public health task, for it is difficult for numerous people.^[20] Neutrophils are the first blood cells that arrive at sites of inflammation. Increase of tumor-associated neutrophils is associated to poor outcome in patients with lung cancer.^[21] Plenty of transverse and longitudinal studies have shown that patients with lung cancer could benefit from quitting smoking; in postoperative patients of lung cancer who continue to smoke, chance of the second tumor can be 2.3 times of quitters, risk of recurrent tumor can be 1.9 times of quitters. Smoking can also increase the incidence of radioactive pneumonia and infection during radiotherapy, and

Table 2. Comparisons of the inflammatory indexes and postoperative outcomes of lung cancer patients among groups of current smokers, ex-smokers and never smokers

Variables	Never-smokers (n=88)	Ex-smokers (n=372)	Current smokers (n=177)	F/X ²	P
WBC [$\times 10^9/L$, mean (SD)]	5.9 (1.4)** [‡]	7.0(2.6)*	7.7(3.4)	13.277	0.000
Albumin [g/L, mean (SD)]	43.2 (3.5)** [‡]	42.1(4.3)*	41.1(4.6)	7.040	0.001
NLR [mean(SD)]	2.8 (1.1)*	3.1(1.9)*	3.7(3.9)	4.727	0.009
PLR [mean(SD)]	132.6 (55.7)	134.9(68.8)	146.7(89.9)	1.625	0.198
Blood loss [mL, mean(SD)]	153.8	186.8	185.2	0.473	0.623
Placement time of closed thoracic drainage tube (days, median)	4	4	6	1.450	0.235
ICU admission days (days, median)	2	2	3	0.963	0.382
In-hospital days (days, median)	9	10	11	0.308	0.735
Hospitalization costs [RMB Yuan, mean(SD)]	60 546.8 (30 060.6)	64 466.8 (33 187.1)	71 072.9 (81 904.9)	1.522	0.219
30-day mortality (%) [#]	1.1	3.0	2.8	0.659	0.743

*compared to the current smoker by *t* test, $P<0.05$; **compared to the current smoker by *t* test, $P<0.01$; [‡]compared to the ex-smoker, $P<0.05$; [‡]compared to the ex-smoker, $P<0.001$. [#] Fishers exact test. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ICU, intensive care unit; WBC, white blood cell.

Table 3. Comparisons of the inflammatory indexes of lung cancer patients and postoperative outcomes of cancer patients among groups of different smoking status and smoking cessation time

Variables	Current smokers (n=88)	Ex-smokers (n=372)					Never-smokers (n=177)	X ² /F*	P*	X ² /F [†]	P [†]
		CeT $\leq$ 6w (n=90)	6w<CeT $\leq$ 1y (n=107)	1y<CeT $\leq$ 5y (n=86)	5y<CeT $\leq$ 10y (n=34)	CeT>10y (n=55)					
WBC [$\times 10^9/L$, mean (SD)]	7.7(3.4)	7.5(2.5)	7.1(3.1)	6.6(2.0)	6.8(2.8)	6.8(2.6)	5.9(1.4)	5.275	0.000	1.362	0.247
Albumin [g/L, mean(SD)]	41.7(4.4)	41.4(3.9)	41.7(5.4)	41.6(4.1)	43.9(3.1)	42.2 (4.0)	43.3 (3.3)	2.470	0.023	2.072	0.084
PLR [mean(SD)]	146.5 (89.9)	117.4 (45.4)	136.9 (75.2)	138.8 (71.3)	147.4 (78.6)	144.7 (73.5)	132.6 (55.7)	1.709	0.116	2.008	0.093
NLR[mean(SD)]	3.7(3.9)	2.9(1.5)	3.2(2.5)	3.1(1.6)	3.2(1.7)	3.3(1.8)	2.8(1.1)	1.697	0.119	0.344	0.848
Blood loss [mL, mean(SD)]	185.2	162.0	159.5	216.8	207.9	219.8	153.8	0.715	0.638	0.336	0.649
Placement time of closed thoracic drainage tube (days, median)	6	5	5	5	4	5	4	0.528	0.787	0.344	0.848
ICU admission days (days, median)	3	2	2	2	2	2	2	0.401	0.878	0.415	0.798
In-hospital days (days, median)	11	11	11	11	8	9	9	0.510	0.801	1.001	0.407
Hospitalization costs [Yuan, mean (SD)]	71 072.9 (81 904.9)	61 959.2 (31 302.4)	63 165.9 (27 290.2)	67 739.4 (36 379.9)	64 668.7 (32 870.4)	63 123.6 (33 953.1)	60 546.8 (30 060.6)	0.599	0.732	0.336	0.854
30-day mortality (%) [#]	2.8	1.1	2.8	2.3	5.9	5.5	1.1	4.768	0.529	3.710	0.406

* compare among the seven groups; [†] compare among the five sub-groups in ex-smoker lung cancer patients. [#] Fisher's exact test.

prolong median survival in small-cell lung cancer patients after radiation and chemotherapy (18.0 months vs. 13.6 months).^[20] Among former smokers with chronic obstructive pulmonary disease (COPD), even after withdrawing cigarette smoking, inflammation persists, lung function continues to deteriorate, and the risk of lung cancer increases.^[22] These facts suggest a strong link between airway inflammation and lung cancer progress.^[21]

Our study found that smoking increased the level of peripheral blood WBC counts and decreased the preoperative albumin level in male patients with lung cancer. The result that preoperative blood WBC count of smokers was higher than that of never-smokers was consistent with previous studies.^[23, 24] The peripheral blood WBC in the current smoker patients before operation was significantly higher than that in the ex-smoker patients, and the latter was higher than that of the never-smoker patients; although there was a decreasing trend in peripheral WBC level of ex-smokers patients with the increasing of cessation time, we did not find significant difference in peripheral blood WBC levels among subgroups of different cessation time. The study of Smith *et al.*^[25] and Lao *et al.*^[26] indicated WBC decreased with increase of smoking cessation time; in study of Peres *et al.*,^[11] WBC level of ex-smokers with 10 years of smoking cessation was close to that of never-smokers after excluding the influence of COPD. Another study on individuals aged 60-79 years old showed that WBC count reverted to that of never-smokers after 20 years of smoking cessation.^[27] In the cohort of this study, lung cancer patients who had quit smoking for longer time were relatively older, which was consistent with previous studies.^[3,28] Therefore, we suggest that smoking impacts preoperative blood WBC greatly in lung cancer patients, and cessation time may not influence WBC to revert to the level of never-smokers. Individual characteristics such as age and contaminant diseases may play a synergetic role.

Smoking significantly decreased serum level of albumin, and after 5 years of smoking cessation, the albumin of smokers basically reached the level of never-smokers. The decrease of serum albumin was suggested to be caused by that cigarette smoking increased urine albumin excretion.^[29,30]

We found that the value of NLR in current smokers was higher than that of never-smokers, which was consistent to the results of Gumus's study that

smoking increased the NLR.^[31] However, the effect of smoking cessation time on NLR has not been reported. Gumus *et al.* also observed that PLR of non-smokers was significantly higher than that of former smokers.^[31] Although in the current study, the PLR value of patients quitting smoking for less than 6 weeks was lower than that of never-smokers, the difference was not significant. Since not enough data have focused on the relationship between smoking cessation and NLR, albumin and PLR, more researches are needed.

The hospitalization costs for smoking lung cancer patients to have surgical treatment was higher than that of never-smokers, and in patients with smoking cessation time over 5 years, the hospitalization costs were basically the same as that of never-smoker patients. Therefore, we suggest patients with lung cancer should be encouraged to quit smoking at any time before operation and as early as possible.

Postoperative mortality is an important index to evaluate the survival time of tumor patients. Studies had found that the mortality rates of lung cancer patients at the 30-day and the 90-day after operation were 1.6% and 3.2%, respectively, and half of the deaths occurred in the period between 31 days and 90 days after discharge.^[32] At present, few study has focused on relationship between preoperative smoking cessation time and postoperative death in patients with lung cancer. In our study, we found that the 30-day mortality rate for the smoking lung cancer patients was 2.9%, which was higher than that of never-smoking patients (1.1%), but the 30-day mortality rate among different groups of smoking status and cessation time were not significantly different. We noticed that the relatively high 30-day mortalities were observed in patients with cessation time longer than 5 years (5.9%, 5.5% respectively), and the average ages of patients with longer cessation time (mean, 64 ys) were older than other group patients. The elderly age of patients with longer cessation time may contribute to the increased 30-day mortality rate.

Some studies have found that smoking is a risk factor for intraoperative and postoperative complications; it increases hospital morbidity/mortality, surgical blood loss, hospitalization costs, *etc.* In our study, we found that the current smoking lung cancer patients had the highest hospitalization costs, while the never-smoking patients had the lowest hospitalization costs, although there was no significant difference among the groups. Besides, the hospitalization costs of

patients who had quit smoking for more than 5 years were comparable to that of never-smoking patients. For operative bleeding, although the never-smoking patients had the lowest amount of intra-operative blood loss (154ml), there was no significant difference among groups of different smoking cessation time; neither was the in-hospital days, ICU admission days, and placement time of closed thoracic drainage tube. It seems that smoking cessation is not related to the perioperative healthcare indicators. However, individual health condition of patients varies and many individual factors can affect the perioperative outcomes greatly; the development of minimally invasive operative technique in lung cancer surgery has improve the surgery related safety. The role of smoking cessation as well as cessation time in surgery healthcare outcome need to be further investigated with careful designation.

There were some limitations in this study. First, as a retrospective study, some valuable laboratory indexes were unavailable, such as serum mean platelet volume which might affect postoperative survival time,^[33, 34] and C-reactive protein (CRP), a inflammatory marker.^[35, 36] Second, as large amounts of patients' contact information were absent, follow up were not effectively carried out, so long-term survival of included lung cancer patients were unable to be analyzed. Third, as the patient cohort came from a single center, there were limitations in patients' sample size and representativeness. Therefore, it is necessary to carry out large-scale multicentric RCT research with long-term survival analysis in future.

Conflicts of interest statement

All authors declared no conflict of interests.

REFERENCES

1. Turan A, Koyuncu O, Egan C, et al. Effect of various durations of smoking cessation on postoperative outcomes: a retrospective cohort analysis. *Eur J Anaesthesiol* 2018; 35(4):256-65. doi: 10.1097/EJA.0000000000000701.
2. McCunniff PT, Young ES, Ahmadinia K, et al. Smoking is associated with increased blood loss and transfusion use after lumbar spinal surgery. *Clin Orthop Relat Res* 2016; 474(4):1019-25. doi: 10.1007/s11999-015-4650-x.
3. Lugg ST, Tikka T, Agostini PJ, et al. Smoking and timing of cessation on postoperative pulmonary complications after curative-intent lung cancer surgery. *J Cardiothorac Surg* 2017; 12(1):52. doi: 10.1186/s13019-017-0614-4.
4. Kamath AS, Vaughan Sarrazin M, Vander Weg MW, et al. Hospital costs associated with smoking in veterans undergoing general surgery. *J Am Coll Surg* 2012; 214(6):901-8. doi: 10.1016/j.jamcollsurg.2012.01.056.
5. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. *Cochrane Database of Syst Rev* 2014; 27(3):CD002294. doi: 10.1002/14651858.CD002294.pub4.
6. Mason DP, Subramanian S, Nowicki ER, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. *Ann Thorac Surg* 2009; 88(2):362-70. doi: 10.1016/j.athoracsurg.2009.04.035.
7. Shiels MS, Katki HA, Freedman ND, et al. Cigarette smoking and variations in systemic immune and inflammation markers. *J Natl Cancer Inst* 2014; 106(11):dju294. doi: 10.1093/jnci/dju294.
8. Blidberg K, Palmberg L, Dahlen B, et al. Increased neutrophil migration in smokers with or without chronic obstructive pulmonary disease. *Respirology* 2012; 17(5):854-60. doi: 10.1111/j.1440-1843.2012.02181.x.
9. Tonstad S, Cowan JL. C-reactive protein as a predictor of disease in smokers and former smokers: a review. *Int J Clin Pract* 2009; 63(11):1634-41. doi: 10.1111/j.1742-1241.2009.02179.x.
10. Shaper AG, Wannamethee SG, Whincup PH. Serum albumin and risk of stroke, coronary heart disease, and mortality: the role of cigarette smoking. *J Clin Epidemiol* 2004; 57(2):195-202. doi: 10.1016/j.jclinepi.2003.07.001.
11. Peres FS, Barreto SM, Camelo LV, et al. Time from smoking cessation and inflammatory markers: new evidence from a cross-sectional analysis of ELISA-Brasil. *Nicotine Tob Res* 2017; 19(7):852-58. doi: 10.1093/ntr/ntx032.
12. Yin Y, Wang J, Wang X, et al. Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: a meta-analysis. *Clinics* 2015; 70(7):524-30. doi: 10.1002/asi.22622.
13. Zhang H, Gao L, Zhang B, et al. Prognostic value of platelet to lymphocyte ratio in non-small cell lung cancer: a systematic review and meta-analysis. *Sci*

- Rep 2016; 6:22618. doi: 10.1038/srep22618.
14. Kasman L, Bolm L, Schild SE, et al. Neutrophil-to-Lymphocyte ratio predicts outcome in limited disease small-cell lung cancer. *Lung* 2017; 195(2): 217-24. doi: 10.1007/s00408-017-9976-6.
 15. Takahashi Y, Kawamura M, Hato T, et al. Neutrophil-lymphocyte ratio as a prognostic marker for lung adenocarcinoma after complete resection. *World J Surg* 2016; 40(2):365-72. doi: 10.1007/s00268-015-3275-2.
 16. Chen P, Wang C, Cheng B, et al. Plasma fibrinogen and serum albumin levels (FA score) act as a promising prognostic indicator in non-small cell lung cancer. *Onco Targets Ther* 2017; 10:3107-18. doi: 10.2147/OTT.S138854.
 17. Minami S, Ogata Y, Ihara S, et al. Pretreatment Glasgow prognostic score and prognostic nutritional index predict overall survival of patients with advanced small cell lung cancer. *Lung Cancer (Auckl)* 2017; 8:249-57. doi: 10.2147/LCTT.S142880.
 18. Knight SB, Crosbie PA, Balata H, et al. Progress and prospects of early detection in lung cancer. *Open Biology* 2017; 7(9):170070. doi: 10.1098/rsob.170070.
 19. Chen LS, Timothy B, Rayjean JH, et al. Genetic risk can be decreased: quitting smoking decreases and delays lung cancer for smokers with high and low CHRNA5 risk genotypes: a meta-analysis. *EBioMedicine* 2016; 11:219-26. doi: 10.1016/j.ebiom.2016.08.012.
 20. Shie HG, Pan SW, Yu WK, et al. Levels of exhaled carbon monoxide measured during an intervention program predict 1-year smoking cessation: a retrospective observational cohort study. *NPJ Prim Care Respir Med* 2017; 27(1):59. doi: 10.1038/s41533-017-0060-8.
 21. Gong L, Cumpian AC, Mauricio DSC, et al. Promoting effect of neutrophils on lung tumorigenesis is mediated by CXCR2 and neutrophil elastase. *Molecular Cancer* 2013; 12(1):154. doi: 10.1186/1476-4598-12-154.
 22. Shapiro SD. End-stage chronic obstructive pulmonary disease. *Am J Respirat Critic Care Med* 2001; 164(3):339-40. doi: 10.1164/ajrccm.164.3.2105072c.
 23. Luetragoon T, Rutqvist LE, Tangvarasittichai O, et al. Interaction among smoking status, single nucleotide polymorphisms, and markers of systemic inflammation in healthy individuals. *Immunology* 2017; 154(1):98-103. doi: 10.1111/imm.12864.
 24. Asthana A, Johnson HM, Piper ME, et al. Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. *Am Heart J* 2010; 160(3):458-63. doi: 10.1016/j.ahj.2010.06.006.
 25. Smith MR, Kinmonth AL, Luben RN, et al. Smoking status and differential white cell count in men and women in the EPIC-Norfolk population. *Atherosclerosis* 2003; 169(2):331-7. doi: 10.1016/S0021-9150(03)00200-4.
 26. Lao XQ, Jiang CQ, Zhang WS, et al. Smoking, smoking cessation and inflammatory markers in older Chinese men: the Guangzhou Biobank Cohort Study. *Atherosclerosis* 2009; 203(1):304-10. doi: 10.1016/j.atherosclerosis.2008.06.028.
 27. Wannamethee SG. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J* 2005; 26(17):1765-73. doi: 10.1093/eurheartj/ehi183.
 28. Groth SS, Whitson BA, Kuskowski MA, et al. Impact of preoperative smoking status on postoperative complication rates and pulmonary function test results 1-year following pulmonary resection for non-small cell lung cancer. *Lung Cancer* 2009; 64(3):352-7. doi: 10.1016/j.lungcan.2008.09.015.
 29. Ekberg G, Grefberg N, Larsson LO. Cigarette smoking and urinary albumin excretion in insulin-treated diabetics without manifest nephropathy. *J Intern Med* 1991; 230(5):435-42. doi: 10.1111/j.1365-2796.1991.tb00469.x.
 30. Yeom H, Lee JH, Kim HC, et al. The association between smoking tobacco after a diagnosis of diabetes and the prevalence of diabetic nephropathy in the Korean male population. *J Prev Med Public Health* 2016; 49(2):108-17. doi: 10.3961/jpmph.15.062.
 31. Gumus F, Solak I, Eryilmaz MA. The effects of smoking on neutrophil/lymphocyte, platelet/lymphocyte ratios. *Bratisl Lek Listy* 2018; 119(2):116-9. doi: 10.4149/BLL_2018_023.
 32. Quero-Valenzuela F, Piedra-Fernández I, Hernández-Escobar F, et al. Half the deaths after surgery for lung cancer occur after discharge. *Surg Oncol* 2018; 27(4):630-4. doi: 10.1016/j.suronc.2018.07.017.
 33. Gao L, Zhang H, Zhang B, et al. Prognostic value of combination of preoperative platelet count and mean platelet volume in patients with resectable non-small cell lung cancer. *Oncotarget* 2017; 8(9):15632-41. doi: 10.18632/oncotarget.14921.
 34. Kumagai S, Tokuno J, Ueda Y, et al. Prognostic signifi-

- cance of preoperative mean platelet volume in resected non-small-cell lung cancer. *Mol Clin Oncol* 2015; 3(1):197-201. doi: 10.3892/mco.2014.436.
35. Tomita M, Ayabe T, Maeda R, et al. Combination of advanced lung cancer inflammation index and C-reactive protein is a prognostic factor in patients with operable non-small cell lung cancer. *World J Oncol* 2017; 8(6):175-9. doi: 10.14740/wjon1076w.
36. Pine SR, Mechanic LE, Enewold L, et al. Increased levels of circulating interleukin 6, interleukin 8, C-reactive protein, and risk of lung cancer. *J Natl Cancer Inst* 2012; 103(14):1112-22. doi: 10.1093/jnci/djr216.