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Prognostic impact of C-reactive protein/albumin ratio on the overall survival of patients with advanced nonsmall cell lung cancers receiving palliative chemotherapy

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Abstract

Recent studies have indicated that the C-reactive protein (CRP)/albumin (CRP/Alb) ratio is associated with clinical outcomes in patients with various carcinomas. However, no studies have explored the association between the ratio of CRP/Alb and clinical outcome of inoperable patients with nonsmall cell lung cancers (NSCLCs). We examined the prognostic impact of CRP/Alb ratio on 165 stage IV NSCLC receiving palliative chemotherapy. The optimal cutoff level of CRP/Alb ratio was set at 0.195. The median follow-up time was 9 months (range, 1–74 months). On univariate analysis, high CRP/Alb ratio (≥0.195) was correlated ($P < .001$) with poorer overall survival (OS). Subgroup analysis of adenocarcinoma showed that CRP/Alb ratio was significantly ($P < .001$) associated with OS. Multivariate analysis showed that CRP/Alb ratio was an independent prognostic factor for OS (hazard ratio: 2.227, $P = .001$). Subgroup analysis revealed that the CRP/Alb ratio had a significant ($P = .001$) prognostic impact on adenocarcinoma patients receiving platinum chemotherapy. Elevated CRP/Alb ratio was significantly associated with male gender ($P = .002$) and smoking history ($P = .009$). The results of this study suggest that the CRP/Alb ratio might be used as a simple, inexpensive, and independent prognostic factor for OS of patients with advanced lung adenocarcinomas receiving platinum chemotherapy.

Abbreviations: CRP = C-reactive protein, CRP/Alb = C-reactive protein/albumin, EGFR = epidermal growth factor receptor, IL-6 = interleukin 6, NSCLC = nonsmall cell lung cancer, OS = overall survival, TNM = tumor, lymph node, and metastasis.

Keywords: albumin, C-reactive protein, C-reactive protein/albumin ratio, nonsmall-cell lung cancer, prognosis

1. Introduction

Nonsmall cell lung cancer (NSCLC) is still increasing in prevalence. It is the leading cause of cancer-related death.[1] A recent study reported that total of 26,093 new lung cancer cases are anticipated in 2017, with more male (18,371/26,093, 70.4%) than female in South Korea.[2] The majority of this disease is usually diagnosed at later stages when curative treatment is unavailable.[1] The benefit of platinum-based doublet chemotherapy, the current standard of care for advanced NSCLC, is only modest.[3] For patients treated with chemotherapy for advanced NSCLC, the 5-year survival rate is less than 5%. They are also at increased risk for chemotherapy toxicity.[4] If we can find new biomarkers for early identification of patients at the greatest risk, we can better select patients who may benefit from aggressive treatment strategies.

Tumor, lymph node, and metastasis (TNM) stage is currently the most reliable tool for determining clinical treatment strategies and predicting the outcome of patients.[5] Although several prognostic biomarkers including maximum standardized uptake value (SUVmax) obtained by 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography,[6] epidermal growth factor receptor (EGFR) status,[7] programmed death-ligand 1,[8] and serum lactate dehydrogenase in advanced NSCLC[9] have been suggested, currently there is no validated biomarker for patients with advanced NSCLC to predict their survival outcome.

Systemic inflammation has long been associated with carcinogenesis, tumor proliferation, and dissemination.[10] It has significant contribution to the prognostic assessment of NSCLC. The prognostic value of many inflammation-based scores such as modified Glasgow Prognostic Score,[11] neutrophil-lymphocyte ratio,[12] and platelet-to-lymphocyte ratio[13] have been validated in NSCLCs. In addition, previous studies have indicated that the levels of serum C-reactive protein (CRP) and albumin correlate with the survival outcome of patients with NSCLCs.[14–18] The prognostic impact of the ratio of CRP/albumin (CRP/Alb) is currently unknown. It may have independent prognostic value. The ratio of CRP/Alb has also been validated as a poor prognostic factor in pancreatic cancer,[19] nasopharyngeal cancer,[20] colorectal cancer,[21] and esophageal cancer.[22] Recent study revealed that the CRP/Alb is an independent predictor for disease progression and death in patients with operable NSCLC[23,24] and in patients with small cell carcinoma.[25] However, no studies have explored the association between the ratio of CRP/Alb and the clinical outcome of inoperable patients with NSCLCs. Therefore, the objective of this

Editor: Eleonore Fröhlich.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:19(e6848)

Received: 24 November 2016 / Received in final form: 10 April 2017 / Accepted: 14 April 2017

http://dx.doi.org/10.1097/MD.0000000000006848

Table 1

Demographic and clinical characteristics of patients.

Characteristic at diagnosis	No. of patients, %
Age, median (range), y	60 (32–82)
Male gender	115 (69.7%)
cT stage	
T1–2	70 (43.8%)
T3–4	90 (56.2%)
cN stage	
N0–1	44 (26.7%)
N2–3	115 (69.7%)
Histologic subtype	
Adenocarcinoma	112 (67.9%)
Nonadenocarcinoma	53 (32.1%)
First-line therapy	
Platinum-based chemotherapy	127 (77%)
Nonplatinum-based	38 (23%)
Smoking history present	113 (68.5%)
ECOG performance status, ≥2	17 (10.3%)

ECOG = The Eastern Cooperative Oncology Group.

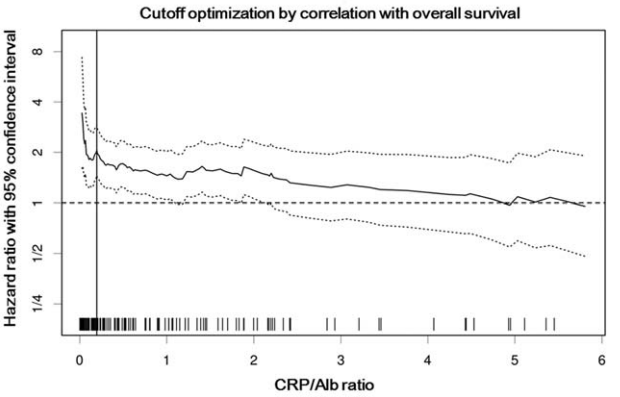

Figure 1. Cutoff optimization by correlation with overall survival (OS) (hazard ratio [HR] with 95% confidence interval on the *y*-axis and C-reactive protein/albumin [CRP/Alb] ratio on the *x*-axis). HR with 95% confidence interval for OS is estimated in patients with high CRP/Alb ratio and in patients with low CRP/Alb ratio. The vertical line indicates the optimal cutoff point with the most significant (log-rank test) split.

retrospective study was to evaluate the prognostic value of the ratio of CRP/Alb in patients with stage IV NSCLC receiving palliative chemotherapy.

2. Materials and methods

2.1. Patient selection

This research was approved by the Institutional Review Board of Ajou University Hospital. Our Institutional Review Board waives the requirement to obtain any informed consent because of retrospective design of our study. We carried out a retrospective study of 165 consecutive patients who received chemotherapy for NSCLC at Ajou University Hospital (Suwon, Republic of Korea) between 2002 and 2011. All patients in this analysis had pathologically or radiologically confirmed stage IV NSCLC and pretreatment blood sampling for CRP and albumin measurement. All patients did not undergo surgery, and only palliative chemotherapy was administered. Patients with detectable inflammatory disease were excluded. Clinicopathologic information including age, gender, clinical TNM stage, histologic subtype, chemotherapic regimen, smoking history, serum CRP, serum albumin, and Eastern Cooperative Oncology Group (ECOG) status were collected retrospectively. The clinical TNM stage was classified on the basis of American Joint Committee on Cancer 7th edition. The CRP/Alb ratio was calculated by dividing the serum CRP level by the serum albumin level. The efficacy assessment was done every 6 weeks. Targeted tumor lesions were assessed with computed tomography scan, magnetic resonance imaging, and bone scan. Tumor response and disease progression were classified according to Response Evaluation Criteria in Solid Tumors (version 1.0).

2.2. Statistical analysis

Overall survival (OS) was defined as the time between the first day of diagnosis and the date of death from any cause. The follow-up of patients who were still alive was censored at their last follow-up date. OS rates were analyzed with Kaplan–Meier curves. They were compared by log-rank testing. Multivariate prognostic analyses were performed on OS with Cox proportional hazards regression model. We included the predictor in the final multivariate analysis if the test had a P value of .05 or less in univariate analysis or if it was a clinically important variable. The enter method of logistic regression was employed to determine the final Cox model for multivariate analysis. The optimal cutoff value of CRP/Alb ratio was determined using an R software-engineered web-based system (http://molpath.charite.de/cutoff/).[26] Categorical variables were compared with Chi-squared test. Data were analyzed using SPSS statistical software program (version 18.0; SPSS Inc, Chicago, IL, USA). All P values are 2-sided associations. Statistical significance was considered when P value was less than .05.

3. Results

3.1. Patient characteristics

The clinical characteristics of the 165 patients included in the study are summarized in Table 1. Patient ages ranged from 32 to 82 years (median: 60 years). Of the 165 patients, 115 were men and 50 were women. By histologic subtyping, 112 had adenocarcinoma and 53 had nonadenocarcinoma. One hundred twenty-seven patients received platinum-based chemotherapy as first-line treatment while the remaining 38 patients received nonplatinum-based chemotherapy. The median follow-up time was 9 months (range: 1–74 months). The median CRP/Alb ratio was 0.41 (range: 0.005–9.716).

3.2. Prognostic significance of CRP/Alb ratio

Using a Biostatistical tool Cutoff Finder, 0.195 was found to be the optimum cutoff point in our study population for CRP/Alb ratio when assessing OS (Fig. 1).[26] Patients were divided into 2 groups based on the cutoff value: CRP/Alb ratio ≥0.195 (n = 108, 65.5%) and CRP/Alb ratio <0.195 (n = 57, 34.5%).

Patients with high CRP/Alb ratio (≥0.195) had lower OS than patients with low CRP/Alb ratio (median OS: 7 vs 16 months, $P < .001$; Fig. 2A). To further assess the additional prognostic information regarding CRP/Alb ratio, we performed subgroup analyses according to histologic subtype. In adenocarcinoma patients, those who had high CRP/Alb ratio had lower OS than

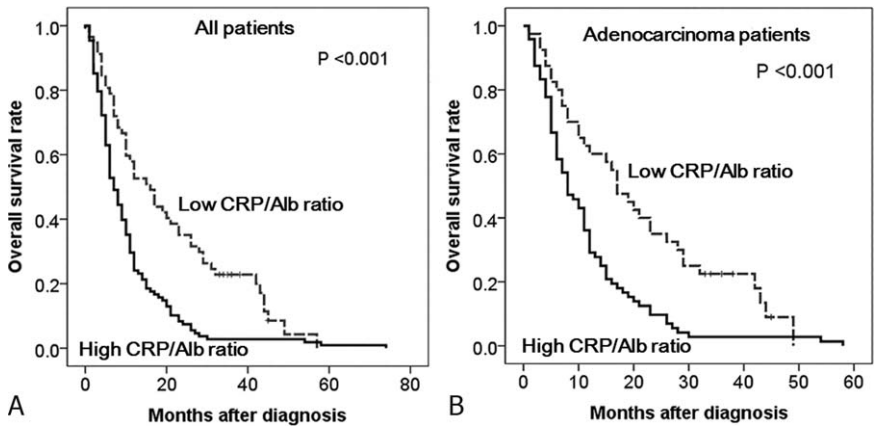

Figure 2. Comparison of survival rates according to the C-reactive protein/albumin (CRP/Alb) ratio and histologic type. Overall survival was significantly worse in patients with CRP/Alb ratio ≥0.195 in all patients (A) and in those with adenocarcinoma (B).

patients with low CRP/Alb ratio (8 vs 17 months, $P < .001$; Fig. 2B). However, there was no association between CRP/Alb ratio and OS in patients with nonadenocarcinoma ($P = .362$).

We then performed subgroup analysis according to chemotherapeutic regimens in adenocarcinoma patients. In patients receiving platinum chemotherapy, those with high CRP/Alb ratio had a lower OS than patients with low CRP/Alb ratio (8 vs 19 months, $P = .001$; Fig. 3A). However, CRP/Alb ratio was not correlated with OS in patients receiving nonplatinum chemotherapy ($P = .503$; Fig. 3B).

Univariate analysis of adenocarcinoma patients revealed that OS was associated with advanced age and clinical nodal stage. Because CRP/Alb ratio has prognostic impact in patients receiving platinum chemotherapy alone, we added chemotherapeutic regimen to multivariate analysis. In multivariate analysis, high CRP/Alb ratio expression was an independent poor prognostic marker for OS in adenocarcinoma (hazard ratio: 2.227, $P = .001$; Table 2).

The clinicopathological characteristics of patients based on CRP/Alb ratio are summarized in Table 3. An elevated CRP/Alb ratio was significantly associated with male gender ($P = .002$) and smoking history ($P = .009$). However, compared to those in the high CRP/Alb ratio group, age ($P = .816$), cT stage ($P = .153$), cN stage ($P = .192$), and ECOG performance status of patients were similar to those in the low CRP/Alb ratio group.

3.3. Tumor response according to CRP/Alb ratio

A total of 89 patients were measured for tumor response. There was no complete response in total patients. Partial response patients was similar in the high CRP/Alb ratio group (n = 10, 17.9%) and the low high CRP/Alb ratio group (n = 5, 15.2%) ($P = .563$; Table 4).

4. Discussion

In the present study, we evaluated the prognostic power of CRP/Alb ratio in patients with stage IV NSCLC receiving palliative chemotherapy. To our knowledge, this is the first study analyzing the correlation between CRP/Alb ratio and OS in inoperable patients with NSCLC. A high CRP/Alb ratio (≥0.195) was found to be an independent poor prognostic factor in patients with adenocarcinoma. The CRP/Alb ratio is a readily available biomarker. It is easy to obtain from serum at diagnosis. It is probably be one of the most inexpensive tests that can be used as a predictive model in cancer.

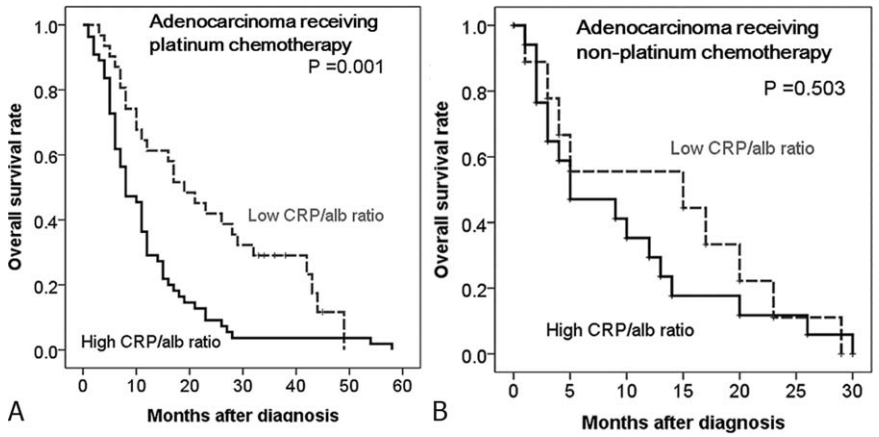

Figure 3. Comparison of survival rates according to the C-reactive protein/albumin (CRP/Alb) ratio and chemotherapeutic regimens. Overall survival (OS) was significantly worse in patients with CRP/Alb ratio ≥0.195 and adenocarcinoma receiving platinum chemotherapy (A). In adenocarcinoma patients receiving nonplatinum chemotherapy (B), there was no significant difference in OS between patients with high CRP/Alb ratio and those with low CRP/Alb ratio.

Table 2

Multivariate analyses of OS in lung adenocarcinoma patients.

Variables	Overall survival		
	HR	95% CI	P
Age (<70 vs ≥70)	2.052	1.139–3.693	.016
Clinical nodal stage (N1vs N2–3)	1.996	1.204–3.308	.007
Chemotherapeutic regimen (platinum vs nonplatinum)	1.520	0.855–2.703	.154
CRP/Alb (<0.195 vs ≥0.195)	2.227	1.371–3.618	.001

CI = confidence interval, CRP/Alb = C-reactive protein/albumin, HR = hazard ratio.

Table 3

Correlation of CRP/Alb ratio with clinical characteristics in adenocarcinoma patients.

Characteristic	CRP/Alb ratio		P
	Low (n = 40)	High (n = 72)	
Age (≥70)	8 (20%)	16 (22.2%)	.816*
Male gender	17 (42.5%)	52 (72.2%)	.002*
cT stage			
T1–2	20 (54.1%)	27 (38.6%)	.153*
T3–4	17 (45.9%)	43 (61.4%)	
cN stage			.192*
N0–1	15 (40.5%)	19 (27.1%)	
N2–3	22 (59.5%)	51 (72.9%)	
Smoking history present	17 (42.5%)	50 (69.4%)	.009*
ECOG performance status (≥2)	2 (5%)	8 (11.1%)	.491†

CRP/Alb = C-reactive protein/albumin; ECOG = The Eastern Cooperative Oncology Group.
* Chi-squared test by 2-sided Pearson exact test.
† Chi-squared test by 2-sided Fisher exact test.

Table 4

Tumor responses.

Response	C-reactive protein/albumin		P
	Low (n = 33)	High (n = 56)	
Complete response	0 (0%)	0 (0%)	.563*
Partial response	5 (15.2%)	10 (17.9%)	
Stable disease	18 (54.5%)	24 (42.9%)	
Progressive disease	10 (30.3%)	22 (39.3%)	
Objective response rate	5 (15.2%)	10 (17.9%)	

* Chi-squared test by 2-sided Fisher exact test.

Chronic inflammation is an emerging hallmark of cancer. It play a key role in carcinogenesis and tumor progression.[27] Increased level of CRP occurs as an inflammatory response secondary to tissue damage induced by infection, trauma, and tumor necrosis.[28] Previous studies have reported that elevated CRP level can affect the growth and progression of cancer.[29,30] CRP binds to phospholipids on membranes of tumor cells, acting as an opsonin, which can lead to lysis of tumor cells.[29] Furthermore, CRP can induce the overexpression of cyclooxygenase-2 enzyme.[29] Persistent inflammatory state produces various inflammatory cytokines including interleukin 6 (IL-6) as a response to tissue necrosis and the presence of tumor cells.[29] IL-6 has an important role in cancer progression. IL-6 can induce malignancy in stem cells from human breast carcinoma.[31] IL-6 is required for the proliferation of breast cancer[32] and colon cancer.[33] IL-6 also contributes to tumor angiogenesis.[34] The level of serum albumin is inversely associated with the magnitude of systemic inflammatory response as a consequence of increased catabolism and downregulation of hepatic synthesis by cytokines tumor necrosis factor alpha and IL-6.[35] Therefore, the levels of albumin and CRP are closely correlated with the levels of IL-6, resulting in cancer progression.

Our results showed that high CRP/Alb ratio was associated with the presence of smoking history. Previous studies have found that increased CRP levels are secondary results of cigarette smoking due to tissue injury.[36,37] Perez-Bautista et al[38] have reported that hypoalbuminemia is also correlated with cigarette smoking.

Although palliative treatment with chemotherapy and radiotherapy provide modest survival benefit for patients with advanced NSCLC, they are associated with severe adverse reactions, including myelosuppression, gastrointestinal reactions, nervous system damage, allergic reactions, liver and kidney damages, and radiation pneumonitis.[39] Therefore, curative effects and treatment-induced adverse reactions should be taken into consideration when chemotherapy and radiotherapy are used. The CRP/Alb ratio may help oncologist select the better treatment plan for patients with advanced NSCLC.

In our study, 77% of the patients received platinum-based combination chemotherapy. Most patients received nonplatinum regimen such as gemcitabine, docetaxel, and paclitaxel in addition to platinum-based regimen. Platinum-based combination chemotherapy is a standard of care for the first-line treatment of metastatic NSCLC.[40] Although gefitinib has been designated as first-line treatment in advanced NSCLC with EGFR mutation,[41] the EGFR test was not widely used at the time of patient treatment of our study.

The limitations of our work include the retrospective nature of the study design and the small sample sizes. Our research can have selective bias or information bias because of the retrospective nature of this study.

In summary, our results suggest that a high CRP/Alb ratio is an independent and poor prognostic factor for patients with advanced lung adenocarcinomas receiving palliative chemotherapy, particularly in the group receiving platinum chemotherapy. Further large-scale studies are needed to determine the effect of CRP/Alb ratio on clinical outcomes of patients with NSCLC and to confirm the present findings.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
[2] Jung KW, Won YJ, Oh CM, et al. Prediction of cancer incidence and mortality in Korea, 2017. Cancer Res Treat 2017;49:306–12.
[3] Le Chevalier T, Scagliotti G, Natale R, et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. Lung Cancer 2005;47:69–80.
[4] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.
[5] Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:300–11.
[6] Jin F, Zhu H, Fu Z, et al. Prognostic value of the standardized uptake value maximum change calculated by dual-time-point (18)F-fluorodeoxyglucose positron emission tomography imaging in patients with advanced non-small-cell lung cancer. Onco Targets Ther 2016;9:2993–9.
[7] Berardi R, Rinaldi S, Santoni M, et al. Prognostic models to predict survival in patients with advanced non-small cell lung cancer treated with first-line chemo- or targeted therapy. Oncotarget 2016;7:26916–24.

[8] Tokito T, Azuma K, Kawahara A, et al. Predictive relevance of PD-L1 expression combined with CD8+ TIL density in stage III non-small cell lung cancer patients receiving concurrent chemoradiotherapy. Eur J Cancer 2016;55:7–14.
[9] Lee DS, Park KR, Kim SJ, et al. Serum lactate dehydrogenase levels at presentation in stage IV non-small cell lung cancer: predictive value of metastases and relation to survival outcomes. Tumour Biol 2016; 37:619–25.
[10] Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493–503.
[11] Kishi T, Matsuo Y, Ueki N, et al. Pretreatment modified Glasgow prognostic score predicts clinical outcomes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2015;92:619–26.
[12] Liu ZL, Zeng TT, Zhou XJ, et al. Neutrophil-lymphocyte ratio as a prognostic marker for chemotherapy in advanced lung cancer. Int J Biol Markers 2016;31:e395–401.
[13] Lee BM, Rodriguez A, Mena G, et al. Platelet-to-lymphocyte ratio and use of NSAIDs during the perioperative period as prognostic indicators in patients with NSCLC undergoing surgery. Cancer Control 2016; 23:284–94.
[14] Gagnon B, Abrahamowicz M, Xiao Y, et al. Flexible modeling improves assessment of prognostic value of C-reactive protein in advanced non-small cell lung cancer. Br J Cancer 2010;102:1113–22.
[15] Arrieta O, Michel Ortega RM, Villanueva-Rodriguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: a prospective study. BMC Cancer 2010;10:50.
[16] Koch A, Fohlin H, Sorenson S. Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. J Thorac Oncol 2009;4:326–32.
[17] Wilop S, Crysandt M, Bendel M, et al. Correlation of C-reactive protein with survival and radiographic response to first-line platinum-based chemotherapy in advanced non-small cell lung cancer. Onkologie 2008;31:665–70.
[18] Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. Curr Oncol Rep 2002;4:250–5.
[19] Liu Z, Jin K, Guo M, et al. Prognostic Value of the CRP/Alb Ratio, a Novel Inflammation-Based Score in Pancreatic Cancer. Ann Surg Oncol 2017;24:561–8.
[20] Zhang Y, Zhou GQ, Liu X, et al. Exploration and validation of C-reactive protein/albumin ratio as a novel inflammation-based prognostic marker in nasopharyngeal carcinoma. J Cancer 2016;7:1406–12.
[21] Shibutani M, Maeda K, Nagahara H, et al. Prognostic significance of the preoperative ratio of C-reactive protein to albumin in patients with colorectal cancer. Anticancer Res 2016;36:995–1001.
[22] Xu XL, Yu HQ, Hu W, et al. A novel inflammation-based prognostic score, the C-reactive protein/albumin ratio predicts the prognosis of patients with operable esophageal squamous cell carcinoma. PLoS One 2015;10:e0138657.
[23] Zhang F, Ying L, Jin J, et al. The C-reactive protein/albumin ratio predicts long-term outcomes of patients with operable non-small cell lung cancer. Oncotarget 2017;8:8835–42.
[24] Miyazaki T, Yamasaki N, Tsuchiya T, et al. Ratio of C-reactive protein to albumin is a prognostic factor for operable non-small-cell lung cancer in elderly patients. Surg Today 2016;[Epub ahead of print].
[25] Zhou T, Zhan J, Hong S, et al. Ratio of C-reactive protein/albumin is an inflammatory prognostic score for predicting overall survival of patients with small-cell lung cancer. Sci Rep 2015;5:10481.
[26] Budczies J, Klauschen F, Sinn BV, et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7:e51862.
[27] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[28] Wang CS, Sun CF. C-reactive protein and malignancy: clinicopathological association and therapeutic implication. Chang Gung Med J 2009;32:471–82.
[29] Groblewska M, Mroczko B, Sosnowska D, et al. Interleukin 6 and C-reactive protein in esophageal cancer. Clin Chim Acta 2012; 413:1583–90.
[30] MacDonald N. Cancer cachexia and targeting chronic inflammation: a unified approach to cancer treatment and palliative/supportive care. J Support Oncol 2007;5:157–62. discussion 164–156, 183.
[31] Sansone P, Storci G, Tavolari S, et al. IL-6 triggers malignant features in mammospheres from human ductal breast carcinoma and normal mammary gland. J Clin Invest 2007;117:3988–4002.
[32] Zacarias-Fluck MF, Morancho B, Vicario R, et al. Effect of cellular senescence on the growth of HER2-positive breast cancers. J Nat Cancer Inst 2015;107:djv020.
[33] Grivennikov S, Karin E, Terzic J, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009;15:103–13.
[34] Huang SP, Wu MS, Wang HP, et al. Correlation between serum levels of interleukin-6 and vascular endothelial growth factor in gastric carcinoma. J Gastroenterol Hepatol 2002;17:1165–9.
[35] Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. J Clin Gastroenterol 2005;39(4 suppl 2): S143–146.
[36] Miller M, Zhan M, Havas S. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors: the Third National Health and Nutrition Examination Survey. Arch Intern Med 2005;165:2063–8.
[37] Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477–82.
[38] Perez-Bautista O, Ramirez-Venegas A, Escobar-Arriaga E, et al. Differences in inflammatory markers in a non-smoking and smoking Mexican population. Rev Invest Clin 2009;61:205–11.
[39] Hamada Y, Naitoh H, Niibe Y, et al. Initial analysis of relationship between plasma platinum concentration and hematological adverse reaction associated with weekly chemotherapy using nedaplatin in combination with radiotherapy for cervical carcinoma. Eur J Gynaecol Oncol 2010;31:517–21.
[40] Heist RS. First-line systemic therapy for non-small cell lung cancer. Hematol Oncol Clin North Am 2017;31:59–70.
[41] Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442–9.