Prognostic Values of Combined Detection of Serum of CRP Kinetics and Initial apoA-I in Advanced NSCLC

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Research

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Abstract

Purpose : This study was to evaluate the value of C-reactive protein (CRP) kinetics and initial apolipoproteinA1 (apoA-I) level as prognostic parameters in advanced non-small Cell Lung Cancer (NSCLC).

Methods: Within a retrospective single-center study, serum CRP and apoA-I level were measured at baseline and at the start of each platinum-based chemotherapy cycle for 125 NSCLC patients. Survival analysis, calculated by the Kaplan–Meier method and log-rank test, was used to assess the prognostic significance of Serum CRP and apoA-I level and both levels. The non-parametric Spearman rank correlation coefficient (rs) was used to measure the correlation between apoA-I and CRP.

Results: Lung cancer-specific survival were significantly different across three CRP kinetics groups (P<0.001), such significant differences were also seen between different apoA-I groups. In multivariate analysis, both CRP kinetics and apoA-I were independent significant factors for overall survival. Patients in non-normalized CRP group with lower apoA-I had a poor prognosis. Spearman's rank correlation analysis revealed that the apoA-I level presented a negative correlation with the CRP level during treatment (r= -2.793, P<0.05).

Conclusion: CRP kinetics and apoA-I may be useful to predict the prognosis of NSCLC patients treated with first-line platinum-based chemotherapy and facilitate individualized treatment.

Introduction

Lung cancer is the leading cause of cancer death and the third most common form of malignancy [1, 2]. Moreover, this disease brought a devastating effect to about 1.6 million people worldwide each year [3]. As we all known, the most common type is non-small cell lung cancer (approximately 85 percent) [4]. More than 65% of patients with this class of lung cancer show locally advanced or metastatic disease [5]. The management of advanced lung cancer has progressed since the introduction of so-called third-generation cytotoxic drugs such as gemcitabine and docetaxel. New drugs such as pemetrexed and molecular targeted drugs were later introduced, while the median overall survival just improved to one more year. Although there are many biomarkers used to predict the survival of NSCLC, their sensitivity and specificity are unsatisfactory. As a result, more accurate biomarkers are still needed to predict the prognosis of NSCLC. Or, combining two or more biomarkers may be a good way.

In clinical studies, an increased level of circulating CRP was found to be associated with shorter survival in patients with several malignancies, such as renal cell carcinoma, multiplemyeloma, melanoma, prostate cancer and gastrointestinal cancer [7–11]. It's also found that a high circulating CRP level in lung cancer patients also indicated shorter survival [12,13]. A study on advanced cancer patients revealed that baseline CRP was an independent prognostic factor for survival in patients with advanced NSCLC receiving palliative first-line chemotherapy [14]. Another available evidence shows that measurement of

CRP both before initiation and during a platinum-based chemotherapy may provide prognostic information for the individual patient with advanced NSCLC. Still, the prognostic role of CRP kinetics and the dynamic changes of CRP concentration, are not completely defined [15]. ApoA-I has been reported as a potential useful biomarker in metastatic nasopharyngeal carcinoma [16]. Nevertheless, few studies have looked into the association between apoA-I and lung cancer, and its prognostic significance remains undefined in NSCLC.

The role of CRP and apoA-I in cancer development remains unclear. Chronic inflammation has been recognized as a key factor that contributes to the development and progression of a variety of malignancies [17]. Elevated levels of pro-inflammatory cytokines, such as interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), and mainly interleukin 6 (IL-6) induces production of CRP in the liver [18, 19]. As we all known, apoA-I has been supposed to be related with tumor necrosis factor-α (TNF-α) [20]. In NSCLC, the tumor cells are able to release IL-6 and TNF-α, as assessed by experimental studies on lung cancer cell lines and expression studies on resected specimens [21, 22]. Thus, NSCLC can induce systemic inflammatory response, and in turn inflammation plays an important role in NSCLC development and progression.

In the present article, we carried out CRP kinetics and initial apoA-I as a single parameter and combination of both to indicate the survival of patients with NSCLC. This may be an accurate tool to assess the prognosis of advanced NSCLC patients.

Materials And Methods

Patients

Between January 2009 and May 2014, 125 participants with advanced NSCLC in the Affiliated Drum Tower Hospital of Nanjing University Medical College.
Eligible criteria as following: (1) patients pathologically confirmed NSCLC with stage □B-□, and no previous or coexisting cancer; (2) none had received therapy before serum collection; (3) patients with concomitant diseases that were associated with increased serum C-reactive protein or decreased serum apoA-I (i.e., inflammation, infectious diseases) were excluded; (4) all patients taking the first-line platinum-based chemotherapy including pemetrexed, gemcitabine or docetaxel plus platinum; (5) patients taking the anti-EGFR drug (gefitinib and erlotinib) during the treatment were excluded; and (6) approved informed written consent.

The number of patients who received first-line therapy with pemetrexed, gemcitabine or docetaxel plus platinum was 72, 42, 11, respectively. The treatment cycle was repeated every 21 days unless disease progression or unacceptable toxicity appeared. The median number of chemotherapy treatment cycles per patient was four (ranging from 1 to 17 cycles). Lung cancer-specific survival was calculated from the first date of chemotherapy to the date of last follow-up or death.

Variables

Detailed clinical and pathological information, including age, gender, smoking history, histology, UICC stage, Eastern Coopertive Oncology Group performance status (ECOG PS), metastasis and overall survival data were available for all patients.

According to the American Joint Committee on Cancer (AJCC) 7th Edition [23], the histologic type was classified into two groups: a SCC (squamous cell carcinoma) group and an adenocarcinoma group. The TNM stage of each carcinoma sample was determined according to the criteria of the WHO and the UICC TNM staging system (7th edition) [24].

Measurements of CRP and apoA-I

The measurements of CRP and apoA-I were performed before and after chemotherapy, and at the time-point when the patients' condition changed. The nadir CRP level was defined as the lowest value during the treatment. Post-treatment apoA-I and CRP level was defined as the value after four cycles first-line platinum-based chemotherapy.

Patients were divided into three groups according to CRP kinetics as previously reported (Fig. 1) [25]. The cutoff point of CRP was set at 5mg/L, with the highest value of 'sensitivity− (1 − specificity)' in the receiver operating characteristics. Patients whose baseline CRP levels were < 5 mg/L were assigned to the non-elevated CRP group. Patients whose baseline CRP levels were ≥ 5 mg/L but normalized (nadir CRP levels of < 5 mg/L) were assigned to the normalized CRP group. Patients whose CRP levels never decreased to a normal level (nadir CRP levels of ≥ 5mg/L) were assigned to the non-normalized CRP group. According to clinic test values of initial apoA-I, 1.00g/l was defined as the cutoff point for dividing 125 patients into normal and lower apoA-I groups.

Statistical Analysis

On the basis of the Fisher's exact test, association between variables was evaluated. Kaplan–Meier method and log-rank test were used for determining overall survival rate and comparing it, respectively. Cox proportional hazards model used to assess predictive parameters. Multivariate predictive accuracy predicting overall survival was quantified with Harrell's concordance index, which represents a modification of the area under the curve (AUC) approach, when censored observations are used as reported elsewhere[26]. The change in the multivariable predictive accuracy related to the inclusion of baseline/nadir CRP level or CRP kinetics status was analyzed, to determine whether baseline/nadir CRP level or CRP kinetics status was a significant predictor of OS. The non-parametric Spearman rank correlation coefficient (rs) was used as a measure of correlation between apoA-I and CRP. $P < 0.05$ was regarded as significant difference. Analysis was performed using SPSS 19.0 statistical software package (SPSS Inc., Chicago, IL). Harrell's concordance index was calculated with R3.0.3 statistical software package.

Results

Patient characteristics and outcome

Patients' characteristics are listed in table 1. All patients were treated with first-line platinum-based chemotherapy. Among 125 patients, 67.2 % men and 32.8 % women. The median age was 56 years (range 38–82). The median follow-up period was 15 months (interquartile range [IQR]: 9.25–26.25 months), 76 % patients died of the disease. Overall survival rates of the 1-year and 2-year for all included patients were 64% and 28.8%, respectively. There was no statistical difference between groups in gender, histology and metastasis.

C-reactive protein kinetics and initial apoA-I

According to CRP kinetics, 68 (54.4%) of the 125 patients had normal baseline CRP levels (non-elevated CRP group). During the follow up period, 34 (59.6%) of the 57 patients with an elevated baseline CRP level normalized at least once (normalized CRP group), while in the remaining 23 patients, CRP levels remained elevated (non-normalized CRP group) (Fig. 1). The median value of apoA-I was 1.03g/L (range 0.36–1.86 g/L) in the whole NSCLC cohort. Normal apoA- I level was shown by 75 (60%) patients, while the remaining (n = 50, 40%) showed a lower apoA-I level.

Gender and histology did not influence CRP kinetics nor apoA-I. Data suggests that non-normalized CRP and lower apoA-I tend to be older, stage 4 and higher ECOG PS, while lower apoA-I tend to be ever-smokers (Table 1). Furthermore, lower apoA-I level was more often in non-normalized CRP group (P< 0.001, Table 2).

Impact of C-reactive protein kinetics and initial apoA-I on survival in NSCLC patients

In table 3, we could find the associations between clinicopathological factors and NSCLC survival. As shown, gender, with absence of smoking history, lower apoA-I, increased baseline CRP, nadir CRP level and CRP kinetics status (normalized CRP and non-normalized CRP) had poor prognosis (Table 2). Furthermore, Cox proportional hazards regression models were used to detect the relationship between survival time and these factors, with results for all patients presented in Table 4. ECOG PS, baseline CRP, nadir CRP, and both of CRP kinetics and initial apoA-I were still significantly associated with NSCLC survival. When baseline/ nadir CRP level and CRP kinetics status were considered separately in multivariate analysis, the predictive accuracy of the model, which included CRP kinetics status, was 85%, higher than that of the model which included baseline/ nadir CRP level (accuracy: 83.7%), showing a gain of 1.3% (Table 4).

Results of Kaplan-Meier survival analyses and log-rank tests are shown in Figs. 2 and 3. For all lung cancer patients (N = 125), there was a statistically significant difference in lung cancer-specific survival across three CRP kinetics groups (P< 0. 001; Fig. 2). Such significant differences of survival time were also seen between the normal apoA-I group (N = 75) and lower apoA-I group (N = 50) (P< 0.001; Fig. 3).

Among all patients, individuals with non-normalized CRP and lower apoA-I had a statistically worse survival outcome, with a hazard ratio of 0.16 [95% confidence interval (CI), 0.08–0.35] and 8.99[95% confidence interval (CI), 4.46–18.11], than those with normal CRP and apoA-I (Table 4).

Correlation of CRP with apoA-I Levels

The correlation of CRP kinetics with initial apoA-I in 125 NSCLC patients are presented in Table 2 (P< 0.001). Lower apoA-I was more frequent in patients of the non-normalized CRP group. We performed the Spearman's rank correlation analysis to confirm the connection between apoA-I and CRP during chemotherapy. The results revealed that the apoA-I and CRP level presented a negative correlation (r= -2.793, P< 0.05) (Fig. 4).

Prognostic Significance of Combining CRP kinetics and initial apoA-I

Additionally, we analyzed the prognostic significance of combining CRP kinetics with initial apoA-I. The results are shown in Fig. 5. The five-year overall survival rates of the four groups were significantly different (P< 0.001). Patients with normalized CRP and normal apoA-I had a significantly higher survival probability than the ones from the other four groups. Conversely, the survival rate of the patients with non-normalized CRP and lower apoA-I (group 5) was the lowest among the five groups. The sequence of the survival rates of the five groups from high to low was group1 > group2 > group3 > group4 > group5.

Discussion

In the present study, we demonstrated that both CRP kinetics and initial apoA-I are useful biomarkers for patients with advanced NSCLC who have received first-line platinumed chemotherapy. CRP kinetics is more accurate than baseline/nadir CRP in predicting prognosis for NSCLC patients, and higher CRP levels accompanied lower apoA-I levels during treatment. Furthermore, we found that combining CRP kinetics with initial apoA-I may enhance prognostic prediction of patients with NSCLC more effectively compared to one variable analysis.

Inflammatory reaction plays a valuable function in tumor origination and development[25]. Circulating leukocytes and CRP always used to evaluating the inflammatory status. A large number of studies have proven that CRP, NLR, PLR, ALB, as poor prognostic indexes in cancers[26–28]. However, compared with other inflammatory predictors, both CRP and CRP kinetics are better independent predictors[29,32–34]. Multiple studies have confirmed that ApoA-1, a prognostic factor plays a role in anti-inflammatory and antioxidant activities in various tumor diseases[30,37]. As we all known, CRP is a strong prognostic predictor in many cancers. As reported previously [14, 33], patients without elevation of pretreatment CRP level have better prognosis than those with elevated pretreatment CRP level. Wilop *et al.* found that normalization of CRP during chemotherapy was associated with better prognosis[15]. Evidence indicates

the prognostic importance of CRP kinetics in various solid cancers[31–34]. CRP kinetics, which comprises the effect of dynamic changes of CRP concentration, has been shown to be more informative than baseline CRP in predicting survival of patients with metastatic renal cell cancer and urothelial carcinoma[25–27], whereas the prognostic value of CRP kinetics in NSCLC patients remains unknown. Additionally, apoA-I also could be an indicator of early epithelial ovarian [35] and pancreatic cancer [36]. Others support this finding and suggest that patients without reduction of pretreatment apoA-I level have better prognosis than those with lower pretreatment apoA-I level [16]. In hepatocellular carcinoma patients, they set up a new score based on serum apolipoprotein A-1 and CRP to predict the OS and DFS. In their retrospective analysis, they found the new score could accurately differentiate the prognosis of HCC patients and is a valuable predictor of OS and DFS [37]. Hence, our study further to prove the predictive value of combination apoA-I and CRP on the survival of NSCLC patients.

In current studies, non-normalized CRP and lower apoA-I tended to be older, stage 4 and higher ECOG PS, while lower apoA-I also tended to be ever-smokers (Table 1), and non-normalized CRP more often in lower apoA-I group (Table 2). In univariate analysis, gender, smoking history, ECOG PS, stage, metastasis, baseline CRP and nadir CRP were shown to be associated with prognosis as well as CRP kinetics and initial apoA-I (Table 3). As the results show, TNM staging doesn't have statistically significant both in univariate and multivariate. We studied patients with advanced NSCLC. If we include people with early stage non-small cell lung cancer, there may be a statistical difference. As mentioned in this paper[37]. Whereas, results from the Cox regression models for all patients showed a more accurate prognostic values of CRP kinetics and initial apoA-I even when adjusting for ECOG PS(Table 4).

Baseline and nadir CRP values of non-normalized CRP groups were significantly higher than those of normalized CRP group. Although both baseline and nadir CRP level were also independent predictors in multivariate analysis, CRP kinetics status was more informative in predicting survival when the predictive accuracy was evaluated between the model including CRP kinetics status or baseline/nadir CRP levels. Our results also demonstrated that CRP kinetics is more accurate than baseline/nadir CRP in predicting prognosis for NSCLC patients. It's showing no difference with previous research[31, 32].

Overall, CRP kinetics and apoA-I can be used as biomarkers for patients with NSCLC. Both biomarkers have been warranted to predict the risk of cancer, to assess tumor aggressiveness and to predict prognosis. The results of the current study indicate that serial measurements of CRP and initial apoA-I are useful to estimate the true status of tumor, to consider adverse effects of continuous cytotoxic chemotherapy, and both could be used as surrogate end points for patients with NSCLC.

The biological foundation for the predictive value of the dynamic changes of CRP and apoA-I level in NSCLC patients remain to be explicit. In an experimental study determined that circulating IL-6, which might be secreted from immune and stromal cells in response to tumor progression [38] or from cancer cells *per se* [39] or both. Afterwords it facilitates tumor cell proliferation and immune invasion [40]. Production of CRP in the liver is strongly induced by pro-inflammatory cytokines such as IL-6 [19,41]. Hence,

CRP could have a crucial role in the presence of systemic inflammatory response in NSCLC could be associated with poor prognosis. Furthermore, apoA-I, which decreased accompanied by elevated proinflammatory cytokines showed in previous studies [42]. Increased expression of IL-6 stimulates the synthesis and secretion of non-pancreatic phospholipase A2 (sPLA2) in the liver during infection and inflammation [43]. Recent studies have found that up-reguletion of sPLA2 reduced the density of apoA-I in transgenic mice [44]. Therefore, decreased the level of apoA-I could be due to the subsequent acute-phase proteins stimulation of elevation of IL-6 during cancer progression. In the present study, we also found that increased CRP level was negatively correlated with lower apoA-I level in NSCLC. Therefore, increment of systemic inflammatory response, as evidenced by increase of serum CRP level and decrease of serum apoA-I level, may be associated with more aggressive behavior of NSCLC. The five-year overall survival rates of the patients with an unnormalized CRP and a low apoA-I level were lowest compared with the other four groups (shown in Fig. 5), whereas, the patients with normal CRP and normal apoA-I had significantly higher survival rates among the five groups. These results have further affirmed the reversed relationship between CRP and apoA-I, moreover, they highlight the prognostic effect of the combining of CRP status and initial apoA-I.

In summary, CRP kinetics and initial apoA-I have an impact on survival in patients with advanced NSCLC treated by first-line platinumed chemotherapy. A normal in CRP level predicts better prognosis, while decrease in apoA-I predicts a worse prognosis. Both CRP and apoA-I, are readily available and inexpensive compared with many new biomarkers that have not been adopted in common use increases the prognostic significance of each alone. Therefore, the use of two determinations, such as CRP and apoA-I, increases the prognostic significance of each alone. Perhaps in non-small cell lung cancer, it is preferable to use a system of two or more determinants to create a prognostic tool for clinicians, as with the use of albumin and beta2-microglobulin in multiple myeloma in the International Prognostic Score (ISS). Similar to previous studies [29,37,45], it was a retrospective, single-institution study with relatively few patients. In order to make up for the deficiencies and improve the research design, the predictive value of CRP kinetics and initial apoA-I would be verified in multicenter prospective studies, with more patients and longer follow-up time.

Conclusion

Our paper have provided powerful proof for both CRP kinetics and initial apoA-I are useful biomarkers for patients with advanced NSCLC. Furthermore, we found that combining CRP kinetics with initial apoA-I may enhance prognostic prediction of patients with NSCLC more effectively compared to one variable analysis. However, our research has some limitations. It was a retrospective, single-institution study with relatively few patients. In future, the predictive value of CRP kinetics and initial apoA-I would be verified in multicenter prospective studies, with more patients and longer follow-up time.

Declarations

Ethics approval and consent to participate

The research was obtained after informed consent in accordance with the Declaration of Helsinki and with approval of the ethical committee of the Affiliated Drum Tower Hospital. Written informed consent was obtained from all patients and/or from the next of kin and caretakers.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no conflict of interest concerning this study.

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Authors' Contributions

CT, JZ, ZD contributed to the design of the study. LJ and HY collected the data. PF and WY conducted the statistical analysis. CT, JZ, LJ contributed to writing of the manuscript. ZD and WY contributed to the revision of the manuscript. All authors approved the final version of the manuscript.

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Not Applicable.

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Figures

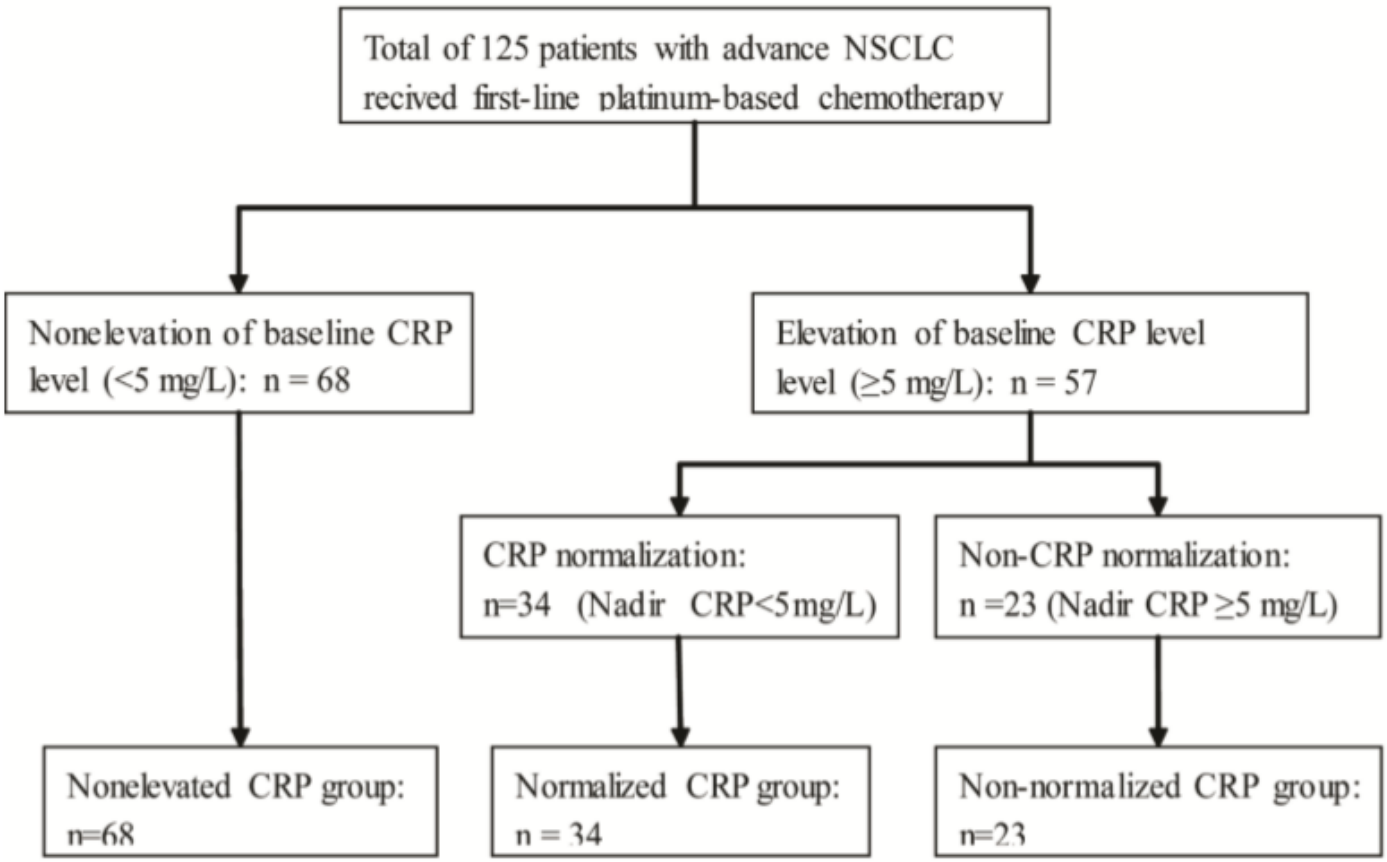

Figure 1

Flow chart of the different patient groups divided according to C-reactive protein kinetics. Platinum-based chemotherapy, pemetrexed/gemcitabine/docetaxel and cisplatin therapy; NSCLC, non-small cell lung cancer; CRP, C-reactive protein.

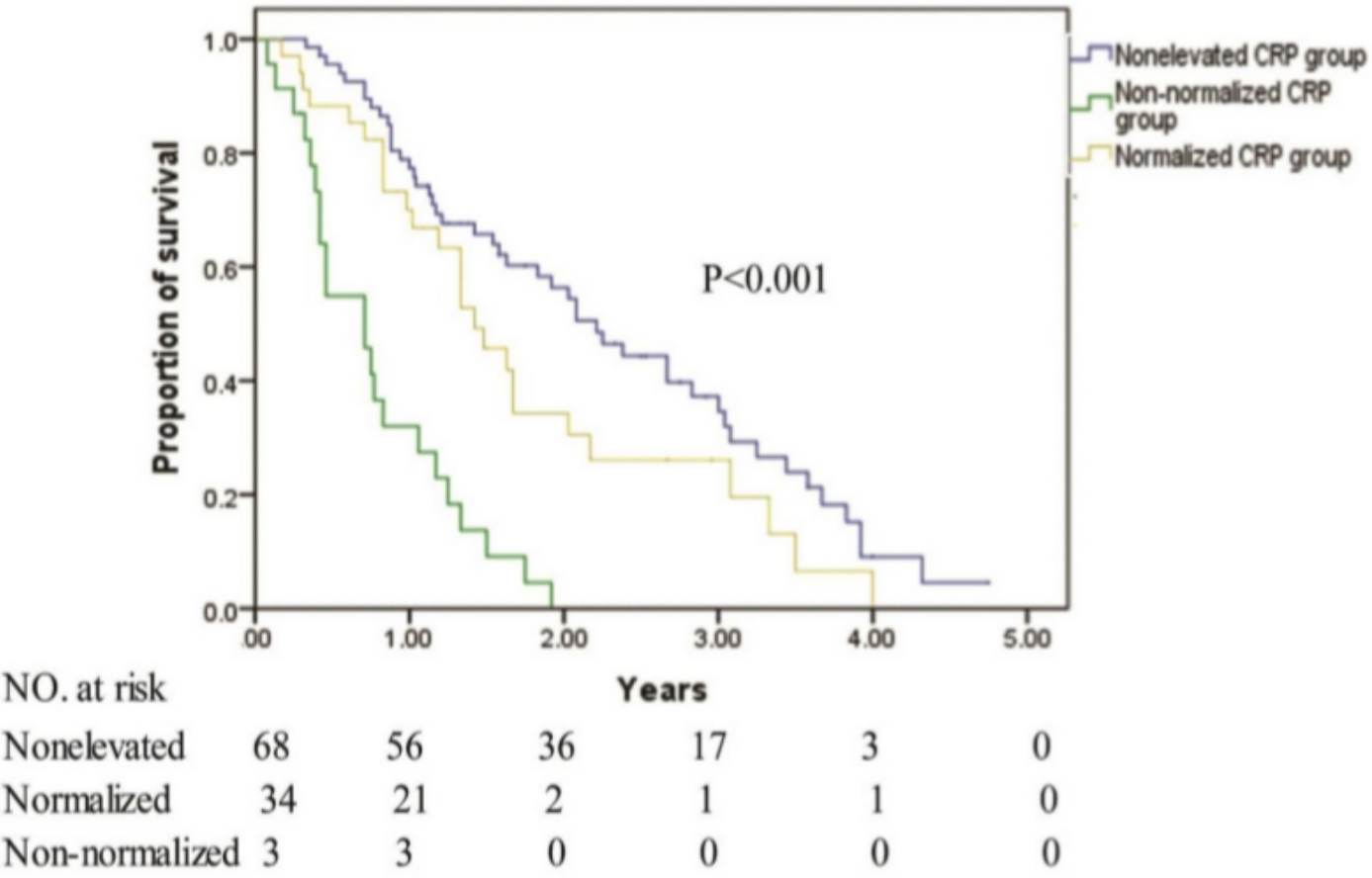

Figure 2

Overall survival curves for total patients with advanced NSCLC according to C-reactive protein (CRP) kinetics.

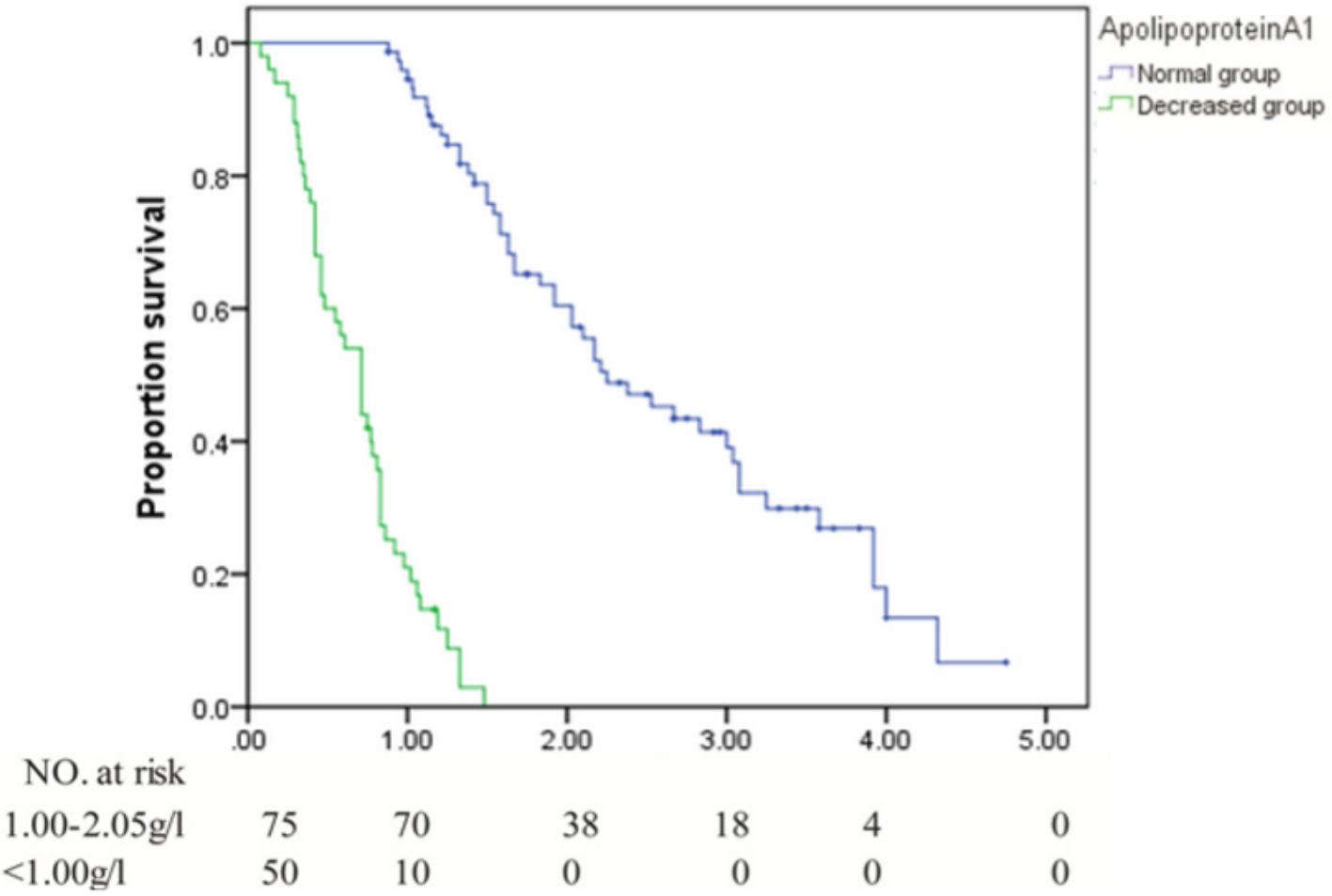

Figure 3

Overall survival curves for all patients with advanced NSCLC according to initial apoA-I level (n=125).

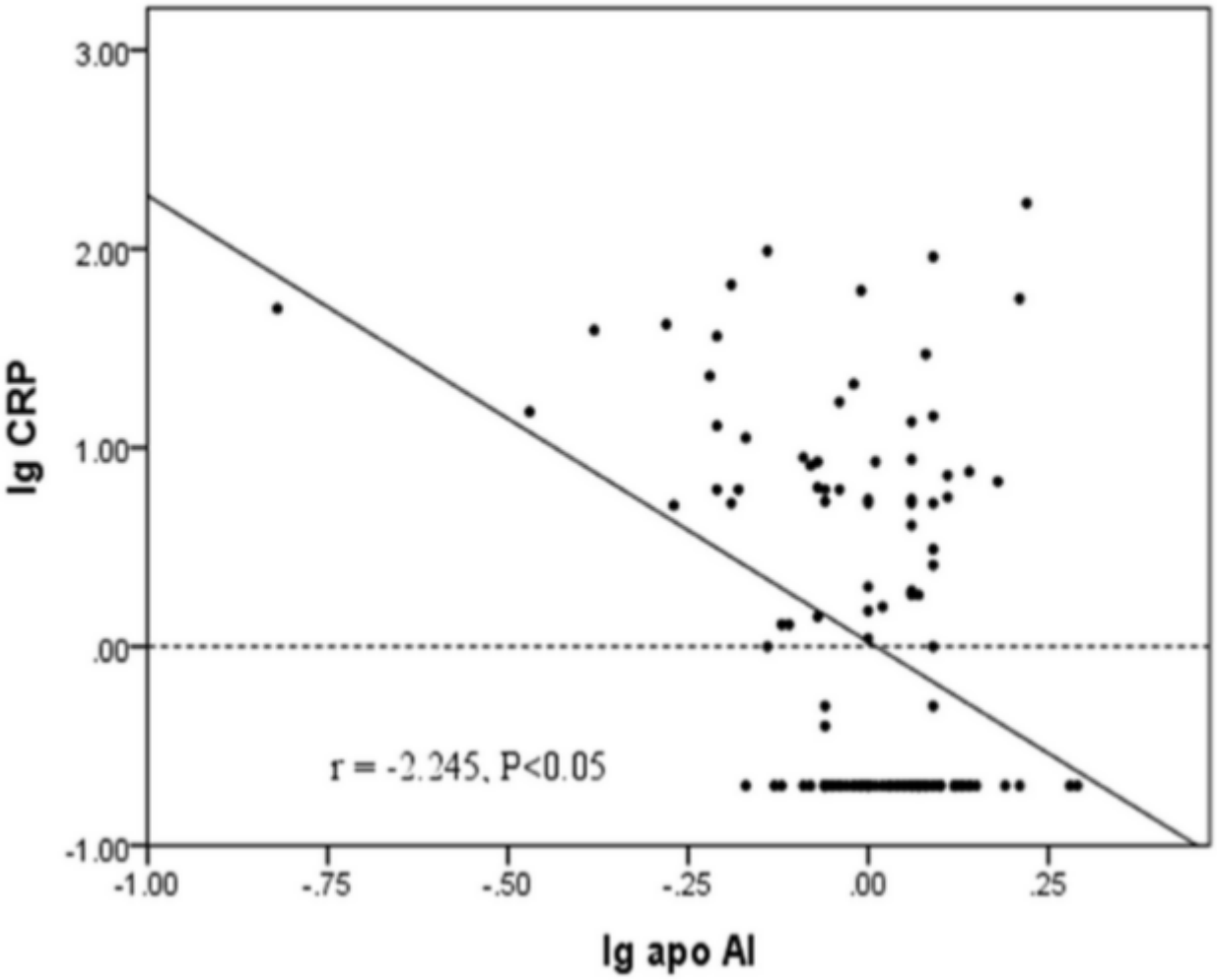

Figure 4

Correlation of serum apoA-I and CRP in 125 patients with NSCLC.

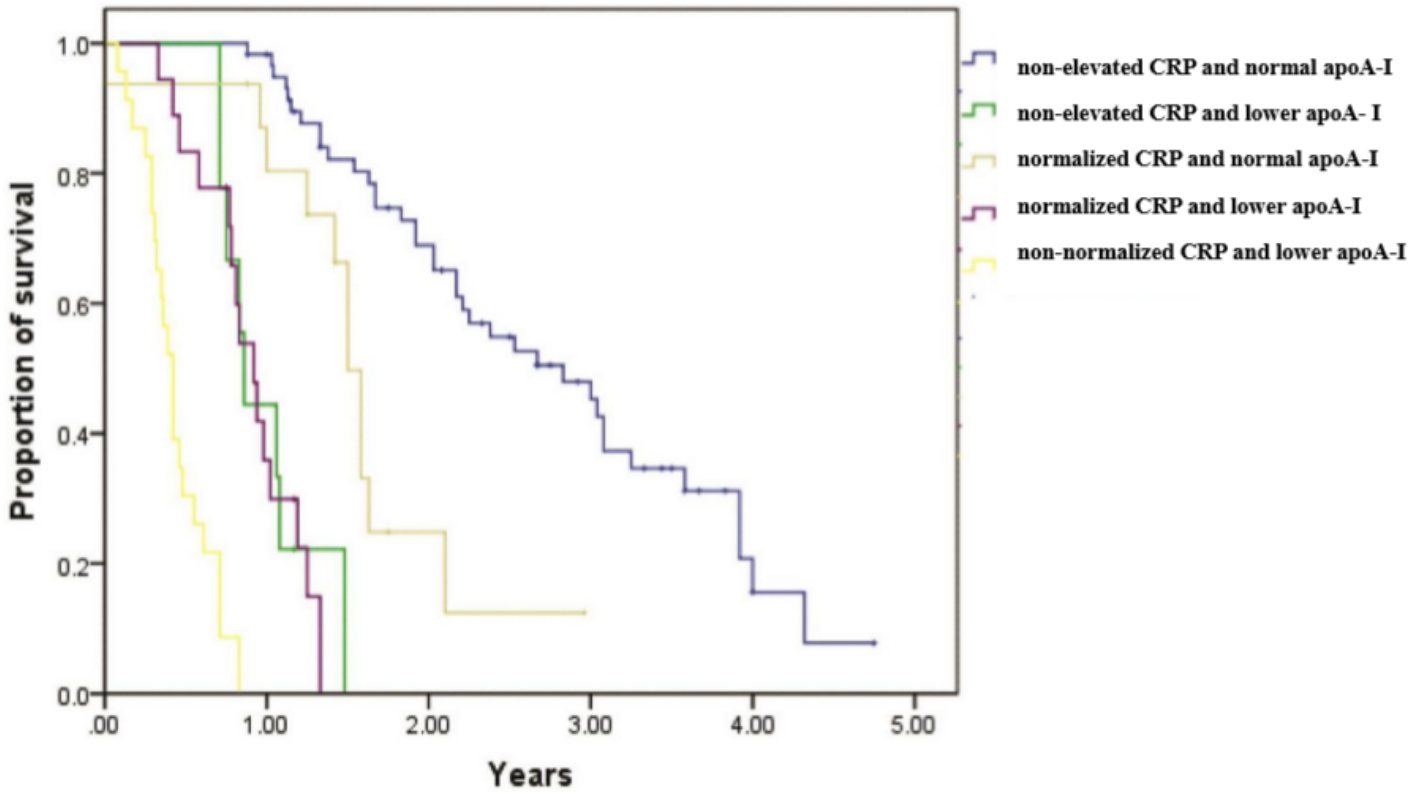

Figure 5

Prognosis significance of combining CRP and apoA-I. The patients were classified to five groups according to CRP kinetics and initial apoA-I (1.00 g/L). Group 1: non-elevated CRP and normal apoA-I; group 2: normalized CRP and normal apoA-I; group 3: non-elevated CRP and lower apoA-I; group 4: normalized CRP and lower apoA-I; group 5: non-normalized CRP and lower apoA-I. The five-years overall survival rates of the five groups were calculated by the Kaplan-Meier method and analyzed by the log-rank test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables01.28.pdf