C-reactive protein as a prognostic marker in chronic obstructive pulmonary disease

ZAI-CHUN DENG1, PENG ZHAO2, CHAO CAO1, SHI-FANG SUN1, FENG ZHAO1, CHAO-YUE LU1 and HONG-YING MA1

1Department of Respiratory Medicine, Affiliated Hospital, School of Medicine, Ningbo University, Ningbo, Zhejiang 315020; 2Department of Internal Medicine, Haining People's Hospital, Haining, Zhejiang 314400, P.R. China

Received July 30, 2013; Accepted December 4, 2013

DOI: 10.3892/etm.2013.1441

Abstract. The present study aimed to evaluate whether circulating C-reactive protein (CRP) levels are a biomarker of systemic inflammation and a significant predictor of future chronic obstructive pulmonary disease (COPD) outcome. During the study, 116 patients with stable COPD and 35 age- and gender-matched healthy subjects with normal pulmonary function were observed. Patient follow-up was also performed to evaluate the strength of the associations between CRP levels and future outcomes. The observations from the present study showed that serum CRP levels were significantly higher in stable COPD patients than in control subjects (4.48±0.83 vs. 1.01±0.27 mg/l, respectively; P<0.05). In addition, it was identified that a serum CRP concentration of >3 mg/l is a poor prognostic variable of COPD compared with a CRP concentration of ≤3 mg/l [hazard ratio (HR), 2.71; 95% confidence interval (CI), 1.05-6.99; P<0.05]. A quantitative synthesis of four studies including 1,750 COPD patients was performed and statistically similar results were obtained (HR, 1.54; 95% CI, 1.14-2.07; P<0.01). The present study showed that circulating CRP levels are higher in stable COPD patients and, therefore, may be used as a long-term predictor of future outcomes. These observations highlight the importance of high sensitivity CRP assays in patients with stable COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality and is predicted to be the third leading cause of mortality worldwide by the year 2020 (1). The most significant risk factor for COPD is cigarette smoking, and for a long time COPD was considered as a consequence of local damage to small airways. However, epidemiological studies have shown that the levels of a serum marker of inflammation, C-reactive protein (CRP), are higher in patients with stable COPD than in healthy controls (2,3). In addition, CRP has been reported as a strong and independent predictor of future outcomes in individuals with COPD (4). Although the hallmark feature of COPD is airflow obstruction, it is poorly predicted by forced expiratory volume in the first second (FEV1) only (5,6). As CRP assays are inexpensive and convenient, CRP levels may be one of the most valuable predictors of outcomes in stable COPD patients. However, currently, CRP levels are usually only determined if an exacerbation of COPD is suspected. The patients included in other specific studies were in the acute exacerbations phase of COPD (7-9). In addition, the association between CRP and mortality in COPD patients remains conflicting rather than conclusive (10-13). It was on this background that the present study was conducted, which aimed to examine whether CRP levels in patients with stable COPD are a significant predictor of prognosis following adjustment for specific prognostic factors.

Materials and methods

Patients. The prospective cohort study included a total of 116 patients that had been diagnosed with COPD ≥6 months previously and had been under treatment for ≥6 months. A diagnosis of COPD was based on medical history, current symptoms and available pulmonary function tests following Global Initiative for Chronic Obstructive Lung Disease guidelines (14). To exclude patients with asthma, subjects with a history of allergic rhinitis or an improvement in FEV1 of >12% from the predicted values following inhalation of a bronchodilator, were not included. Patients with evidence of extensive pulmonary tuberculosis, malignancy or who were suffering from psychosis were excluded from the study. All patients with COPD were clinically stable and none had a history of respiratory infection for at least a 4-week period preceding the study. Approval for this study was obtained from the Institutional Review Board for Human Studies of Affiliated Hospital, School of Medicine, Ningbo University.
(Ningbo, China) and informed consent was obtained from all participating subjects.

**CRP measurement.** Fasting blood samples were obtained from the patients whilst at rest, prior to any other test being performed. Serum CRP levels were measured by high sensitivity immunoturbidimetry (Beckman Coulter, Inc., Miami, FL, USA). The results were given in units of mg/l and the analytical sensitivity of this analysis was 0.1 mg/l. The cutoff point for the CRP concentration was 3 mg/l, as indicated in previous studies (10,11,15).

**Follow-up.** The study was conducted between August 2009 and April 2012, with a follow-up of 32 months or until patient mortality. The follow-up was carried out by telephoning the patients or their next of kin and/or checking hospital records. Critical events were recorded by the physicians in charge of the follow-ups. Subjects who were not located at follow-up and were not known to have succumbed to their illness were considered as censored at the end of the study period.

**Statistical Analysis.** The continuous variables are presented as mean ± SD and the categorical variables are presented as absolute numbers and percentages. Cox regression analysis was used to examine time to COPD mortality using hazard ratios (HR) and 95% confidence intervals (CIs). Risk measures were adjusted for age, gender, FEV1% pred, smoking and presence of disease. Kaplan-Meier mortality curves were created to exhibit differences in mortality by selected risk factors. Quantitative synthesis of all relevant studies was performed and the methods used have been described in detail in previous studies (16,17). The HRs of time-to-event data were directly extracted from the original study or were read off survival curves to estimate the logHR and its variance, as suggested by Parmar et al (18). The statistical analyses were performed using SPSS, version 13.0 (SPSS, Inc., Chicago, IL, USA) and Review Manager 5.0.17 (Cochrane Library Software, Oxford, UK). Two-tailed P<0.05 was considered to indicate a statistically significant difference.

**Results**

A total of 116 consecutive COPD patients (including 75 males) were recruited into the study, as well as 35 healthy subjects (including 18 males) aged over 50 years, with no evidence of COPD. The healthy subjects were randomly selected from a population sample of subjects living in the same area as the COPD population. The healthy subjects were randomly selected from a healthy population sample of subjects living in the same area as the COPD. The healthy subjects were randomly selected from a healthy control group, comprising the current study and three published studies, was conducted between August 2009 and April 2012, with a follow-up of 32 months or until patient mortality. The follow-up was carried out by telephoning the patients or their next of kin and/or checking hospital records. Critical events were recorded by the physicians in charge of the follow-ups. Subjects who were not located at follow-up and were not known to have succumbed to their illness were considered as censored at the end of the study period.

**Follow-up.** The study was conducted between August 2009 and April 2012, with a follow-up of 32 months or until patient mortality. The follow-up was carried out by telephoning the patients or their next of kin and/or checking hospital records. Critical events were recorded by the physicians in charge of the follow-ups. Subjects who were not located at follow-up and were not known to have succumbed to their illness were considered as censored at the end of the study period.

**Statistical Analysis.** The continuous variables are presented as mean ± SD and the categorical variables are presented as absolute numbers and percentages. Cox regression analysis was used to examine time to COPD mortality using hazard ratios (HR) and 95% confidence intervals (CIs). Risk measures were adjusted for age, gender, FEV1% pred, smoking and presence of disease. Kaplan-Meier mortality curves were created to exhibit differences in mortality by selected risk factors. Quantitative synthesis of all relevant studies was performed and the methods used have been described in detail in previous studies (16,17). The HRs of time-to-event data were directly extracted from the original study or were read off survival curves to estimate the logHR and its variance, as suggested by Parmar et al (18). The statistical analyses were performed using SPSS, version 13.0 (SPSS, Inc., Chicago, IL, USA) and Review Manager 5.0.17 (Cochrane Library Software, Oxford, UK). Two-tailed P<0.05 was considered to indicate a statistically significant difference.

**Data presented as mean ± SD, n or %, unless otherwise indicated.**

**Table I. Baseline characteristics of the study participants.**

| Characteristics | COPD patients n=116 | Healthy controls n=35 | P-value |
|-----------------|---------------------|-----------------------|---------|
| Gender          |                     |                       | 0.16    |
| Male            | 75                  | 18                    |         |
| Female          | 41                  | 17                    |         |
| Age, years      | 71.0±9.0            | 68.9±5.1              | 0.09    |
| BMI, kg/m²      | 24.6±3.2            | 25.8±5.7              | 0.12    |
| Smoking status  |                     |                       | 0.13    |
| Current smoker  | 46                  | 14                    |         |
| Ex-smoker       | 34                  | 5                     |         |
| Never           | 36                  | 16                    |         |
| FEV1, % predicted | 44.7±12.1          | 90.4±6.8              | <0.001  |
| Inhaled steroid, % | 61.2               |                       |         |
| β2-agonist, %   | 61.2                |                       |         |
| Inhaled ipratropium, % | 53.4               |                       |         |
| Theophylline, % | 36.2                |                       |         |
| Comorbid illnesses, n |       |                       |         |
| 0               | 36                  |                       |         |
| 1               | 52                  |                       |         |
| 2               | 15                  |                       |         |
| 3               | 10                  |                       |         |
| 4               | 3                   |                       |         |
| CRP, mg/l       | 4.48±0.83           | 1.01±0.27             | 0.025   |

At the end of follow-up, 21 patients had succumbed (18%). However, information concerning the cause of mortality of four patients was not available since contact details had been changed or through lack of cooperation from the patients' families. When CRP ≤3 mg/l was used as the reference category, values >3 mg/l were associated with increased mortality (HR, 2.71; 95% CI, 1.05-6.99; P<0.05). Kaplan-Meier survival curves for all-cause mortality, according to CRP categories, are shown in Fig. 1. The clinical parameters between survivors and nonsurvivors were also compared. Compared with survivors, nonsurvivors had a high degree of airflow obstruction (FEV1% pred, 40.5±17.9 vs. 54.6±18.0, respectively; P<0.05) and CRP concentration (7.56±5.18 vs. 3.48±6.55 mg/l, respectively; P<0.05). However, no significant difference in age, gender and BMI was observed between the two groups.

In addition, a quantitative synthesis of four studies, comprising the current study and three published studies, was performed (10,11,15). Among these studies, the median duration of the follow-ups ranged between 3 and 10 years. Risk measures were frequently adjusted for age, gender, FEV1% pred and smoking. As shown in Fig. 2, the HR of mortality in
patients with a CRP >3 mg/l was 1.54 (95% CI, 1.14-2.07) compared with those with CRP ≤3 mg/l.

Discussion

The present study was performed to evaluate whether circulating CRP levels are a biomarker of systemic inflammation and a significant predictor of future COPD outcomes. In this study, serum CRP levels were found to be significantly higher in stable COPD patients than in well-matched healthy control subjects. The results obtained are consistent with previous studies, indicating the presence of systemic inflammation in patients with stable COPD (2,3).

A number of independent predictors of future COPD outcomes have been identified previously, including exercise capacity (19), biomarkers of systemic inflammation (20), BMI (21,22), smoking status (23), severity of dyspnea (24), FEV1 (5) and PaO2 (23). Among these, the best studied and most convenient to evaluate is serum CRP levels.

The present study showed that increased serum CRP levels are a strong predictor of COPD mortality. Liu et al determined that a serum CRP concentration of >3 mg/l was a poorer prognostic variable of COPD compared with a CRP concentration ≤3 mg/l (11). In the study by Dahl et al, the HR of mortality due to COPD was 2.2-fold higher in patients with a high CRP level than in those with a low CRP level (15). The observations in the present study are in agreement with these studies. However, de Torres et al reported that CRP levels are not associated with survival status (10).

Considering the inconsistent results between previous studies, a quantitative synthesis of the evidence, using rigorous methods, was performed. Meta-analysis was conducted on four studies with 1,750 subjects to evaluate the association between serum CRP levels and mortality in patients with COPD. This meta-analysis indicated that a high level of serum CRP is associated with an increased risk of mortality in COPD patients.

At present, CRP levels are only determined if an exacerbation of COPD is suspected. The results of the present study have several implications, showing that stable COPD patients had a higher level of CRP than healthy controls, indicating the presence of systemic inflammation in patients with stable COPD (2,3).

A number of independent predictors of future COPD outcomes have been identified previously, including exercise capacity (19), biomarkers of systemic inflammation (20), BMI (21,22), smoking status (23), severity of dyspnea (24), FEV1 (5) and PaO2 (23). Among these, the best studied and most convenient to evaluate is serum CRP levels.

The present study showed that increased serum CRP levels are a strong predictor of COPD mortality. Liu et al determined that a serum CRP concentration of >3 mg/l was a poorer prognostic variable of COPD compared with a CRP concentration ≤3 mg/l (11). In the study by Dahl et al, the HR of mortality due to COPD was 2.2-fold higher in patients with a high CRP level than in those with a low CRP level (15). The observations in the present study are in agreement with these studies. However, de Torres et al reported that CRP levels are not associated with survival status (10).
COPD outcomes in individuals with airway obstruction. These observations highlight the significance of high sensitivity CRP assays in patients with stable COPD.

Acknowledgements

This study was partly supported by grants from the Social Development Science and Technology Project (no. 2011C50025), Natural Science Foundation (no. 2012A610257) and the Social Development Science and Technology Project of Ningbo (no. 2011C50073).

References

1. Murray CJ and Lopez AD: Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 349: 1269-1276, 1997.
2. Karadag F, Kirdar S, Karul AB and Ceylan E: The value of C-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. Eur J Intern Med 19: 104-108, 2008.
3. He Z, Chen Y, Chen P, Wu G and Cai S: Local inflammation occurs before systemic inflammation in patients with COPD. Respirology 15: 478-484, 2010.
4. Man SF, Connell JE, Amhonsen NR, Wise RA, Tashkin DP and Sin DD: C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 61: 849-853, 2006.
5. Waschki B, Kirsten A, Holz O, et al: Physical activity is the strongest predictor of all-cause mortality in patients with chronic obstructive pulmonary disease: a prospective cohort study. Chest 140: 331-342, 2011.
6. Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350: 1005-1012, 2004.
7. Stolz D, Christ-Crain M, Morgenthaler NG, et al: Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest 131: 1058-1067, 2007.
8. Murphy SA, Haja Mydin H, Fatah S and Antunes G: Predicting end-of-life in patients with an exacerbation of COPD by routine clinical assessment. Respir Med 104: 1668-1674, 2010.
9. Lacoma A, Prat C, Andreo F, et al: Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 6: 157-169, 2011.
10. de Torres JP, Pinto-Plata V, Casanova C, et al: C-reactive protein levels and survival in patients with moderate to very severe COPD. Chest 133: 1336-1343, 2008.
11. Liu SF, Wang CC, Chin CH, Chen YC and Lin MC: High value of combined serum C-reactive protein and BODE score for mortality prediction in patients with stable COPD. Arch Bronconeumol 47: 427-432, 2011.
12. Miniati M, Monti S, Bottai M, Cocci F, Fornai E and Labravo V: Prognostic value of C-reactive protein in chronic obstructive pulmonary disease. Intern Med 6: 423-430, 2011.
13. Man SF, Xing L, Connell JE, et al: Circulating fibronectin to C-reactive protein ratio and mortality: a biomarker in COPD? Eur Respir J 32: 1451-1457, 2008.
14. Rabe KF, Hurst S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176: 532-555, 2007.
15. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A and Nordestgaard BG: C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175: 250-255, 2007.
16. Cao C, Fang JJ, Ying T, et al: Vascular endothelial growth factor +936C/T and +405G/C polymorphisms and cancer risk: a meta-analysis. Arch Med Res 41: 548-557, 2010.
17. Cao C, Ying T, Fang JJ, et al: Polymorphism of vascular endothelial growth factor -2578C/A with cancer risk: evidence from 11263 subjects. Med Oncol 28: 1169-1175, 2011.
18. Parmar MK, Torri V and Stewart L: Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17: 2815-2834, 1998.
19. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J and Lange P: Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J 20: 539-544, 2002.
20. Schembri S, Anderson W, Morant S, et al: A predictive model of hospitalization and death from chronic obstructive pulmonary disease. Respir Med 103: 1461-1467, 2009.
21. Coxson HO, Chan IH, Mayo JR, Hlynksy J, Nakano Y and Birmingham CL: Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med 170: 748-752, 2004.
22. Cao C, Wang R, Wang J, Bunjoo H, Xu Y and Xiong W: Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. PLoS One 7: e43892, 2012.
23. Nizet TA, van den Elshout FJ, Heijdra YF, van de Ven MJ, Mulder PG and Folgering HT: Survival of chronic hypercapnic COPD patients is predicted by smoking habits, comorbidity, and hypoxemia. Chest 127: 1904-1910, 2005.
24. Nishimura K, Izumi T, Tsukino M and Oga T: Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 121: 1434-1440, 2002.