High sensitive C-reactive protein for prediction of adverse outcome in acute exacerbation of chronic obstructive pulmonary disease

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Abstract

Hospitalization for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with a high risk of mortality and complications. The goal of the study is to assess the clinical utility of serum high sensitive C-reactive protein (hs-CRP) at admission in predicting outcome in hospitalized patients with AECOPD. ***Methods:*** *Consecutive patients with AECOPD admitted to a public teaching hospital were studied prospectively. The adverse outcome defined occurrence of one or more of: (1) death in hospital or within 30 days after discharge, (2) transfer to the intensive care unit, or (3) intubation and mechanical ventilation. The correlation of hs-CRP with duration of hospitalization and FEV1% of predicted is also calculated.* ***Results:*** *Of 60 patients, 22 had adverse outcome and 38 good outcomes. There were no significant differences between two group for mean age, gender, smoking status, and previous hospitalizations (p>0.05). The adverse outcome rate was 56.5% in those with serum hs-CRP equal or more than 100 mg/ml versus 24.3% in patients with hs-CRP less 100 mg/ml (p=0.01).* ***Conclusions:*** *Serum hs-CRP at admission is a predictor of outcome in AECOPD. Admission hs-CRP higher than 100 mg/ml was associated with near fourfold increased probability of adverse outcome.*

Keywords: *Chronic obstructive pulmonary disease, exacerbation, outcome, prediction, hs-CRP*

Rezumat

Proteina C reactivă înalt senzitivă ca predictor al evoluției nefavorabile la pacienții cu exacerbare acută a bronhopneumopatiei cronice obstructive

Spitalizarea pentru exacerbarea acută a bronhopneumopatiei cronice obstructive (EABPOC) se asociază cu un risc crescut de mortalitate și complicații. Scopul studiului a fost de a evalua utilitatea clinică a nivelului seric al proteinei C reactive înalt senzitive (hs-CRP) la internare pentru predicția evoluției la pacienții internați cu EABPOC. ***Metodă:*** *Pacienții consecutivi internați cu EABPOC într-un spital public universitar au fost studiați prospectiv. Evoluția nefavorabilă a fost definită ca apariția uneia sau a mai multor dintre următoarele eventualități: (1) decesul în spital sau în decursul a 30 de zile după externare; (2) transfer în secția de terapie intensivă și/sau intubație și ventilație mecanică, (3) reinternarea pentru BPOC în următoarele 30 de zile. S-au calculat și corelațiile dintre hs-CRP și durata de spitalizare și VEMS % din prezis.* ***Rezultate:*** *Din 60 de pacienți, 22 au avut evoluție nefavorabilă și 38 evoluție favorabilă. Nu au existat diferențe semnificative între cele două grupuri în privința vârstei medii, genului, statutului de fumător și spitalizărilor anterioare (p>0.05). Rata evoluției nefavorabile a fost de 56,6% la cei cu nivel seric al hs-CRP egal sau mai mare de 100 mg/ml, față de 24,3% la pacienții cu hs-CRP sub 100 mg/ml (p=0.01).* ***Concluzii:*** *Nivelul seric al hs-CRP la internare este un predictor al evoluției în EABPOC. Un nivel al hs-CRP peste 100 mg/ml s-a asociat cu o probabilitate de aproape patru ori mai mare pentru evoluția nefavorabilă.*

Cuvinte-cheie: *bronhopneumopatie cronică obstructivă, exacerbare, evoluție, predicție, hs-CRP*

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease and Global Initiative for Chronic Obstructive Lung Disease (GOLD) estimated it will be the third most common cause of death by 2020[1]. Acute COPD exacerbation (AECOPD) contributes to hospital admissions, health-care costs and mortality[1-2].

The mortality rate for patients admitted for an AECOPD is about 10% in-hospital, and near one-third in the year after hospitalization[3].

Recent evidence is suggestive that COPD is a chronic systemic inflammatory disorder. C-reactive protein (CRP), a marker of inflammation, is used as a predictor of long-term morbidity and mortality in patients with coronary heart disease, chronic renal failure[4,5] , stroke[6], sepsis[7], and acute pancreatitis [8].

CRP is related to long-term mortality in stable COPD patients[3, 9-10].

However, standard assays for CRP, with a lower detection limit of 3–8 mg/L, lack the sensitivity required to determine levels of inflammation within the normal range[11,12].

Highly sensitive assays for CRP (hs-CRP) are available for detection of low grade inflammation. It is used in cardiovascular disease and diabetes mellitus[11,13-14]. Recently, its value in AECOPD is considered[3].

The objective of this study was to determine whether the measurement of hs-CRP at admission is useful in predicting adverse outcomes in patients with AECOPD.

Material and methods

Setting and study design

This prospective cohort study is conducted in patients admitted for AECOPD to the respiratory diseases ward, Urmia Imam Khomeini Hospital, a tertiary referral center in Iran.

Table I Demographic characteristics of the two groups of patients (with good and adverse outcome)

	Good outcome n=38	Adverse outcome n=22	P value
Age: years (mean ±SD)	67.84±9.32	72.13±9.54	0.094
Gender: Male/female	25/13	15/7	0.850
Previous exacerbation Yes/No	26/12	18/4	0.258
Smoking: Yes/No	26/12	18/4	0.258
Bread cooking: Yes/No	14/21	7/15	0.694

Patients

Inclusion criteria were: The diagnosis of AECOPD, defined as an acute change in the patient's baseline dyspnea, cough and/or sputum production, severe enough to seek medical attention to hospital[2]. The post-bronchodilator spirometric values met the GOLD criteria for COPD diagnosis.

Patients with any known diseases that could cause CRP elevation or presenting with new infiltrates on the chest X-ray were excluded.

The following variables were recorded: 1. demographics: age, gender, smoking status, history of bread cooking with biomass fuels; 2. presence and number of AECOPD hospitalizations during the past year; a chest X-ray was performed at admittance to exclude the presence of pneumonia; 3. spirometry: a current and post-bronchodilator forced expiratory volume in first second (FEV1) by using a spirometer (Spirolab II, Italy); 4. duration of hospitalization.

The outcomes of the patients and their complications were collected during hospitalization and 30 days after discharge.

Adverse outcome was defined by the presence of at least one of the following outcomes: (I) death in hospital or within 30 days after discharge, (II) need for ICU transfer, and/or need for intubation or mechanical ventilation, and (III) hospitalization for COPD in any hospital within 30 days after discharge.

Measurement of serum levels of hs-CRP:

A 5 ml blood sample was obtained from each subject and centrifuged at 2,000 g for 15 minutes. Serum was separated, aliquoted and stored at -80°C until analysis. Serum levels of hs-CRP were measured with a commercial enzyme-linked immunosorbent assay (ELISA) kit from Diagnostics Biochem Canada Inc. according to the manufacturer's instructions.

Statistical analysis

Data were analyzed by using SPSS version 18.0. *P*-values less than 0.05 were considered statistically significant. Data are presented as the means± SD. Student's *t* test was used to compare continuous variables.

Results

Sixty patients were hospitalized with AECOPD, among them 22 had adverse outcome and 38 good outcome, considered as explained above. The demographic characteristics of the patients in the two groups are shown in Table I. There were no significant differences for mean age, gender, and smoking status or bread cooking with biomass fuels (p value>0.05 for all variables).

Table II Adverse outcome rate in patients with hs-CRP higher and less than 100 mg/ml

	Good outcome n (%)	Adverse outcome n (%)	Total n	P value	odds ratio (CI)
hs-CRP <100 mg/ml	28 (75.7%)	9 (24.3%)	37	0.01	4.044 (1.32-12.33)
hs-CRP ≥100 mg/ml	10 (43.5%)	13 (56.5%)	23		

Mean serum hs-CRP levels in mg/L (mean± SD) were 94.89±32.48 and 66.85±43.74 in adverse outcome and good outcome group respectively, with a significant difference between the two groups (p value = 0.010).

Table II shows adverse outcome rate in patients with hs-CRP higher than and inferior to a threshold value of 100 mg/ml.

Serum levels of hs-CRP higher than 100 mg/ml at admission were associated with a fourfold higher risk of adverse outcome.

Figure 1 shows that serum hs-CRP level was negatively correlated with FEV1 and positively with duration of hospitalization.

Discussion

This study showed that the level of hs-CRP at admission in patients with AECOPD is a prognostic factor. Serum levels of hs-CRP higher than 100 mg/ml at admission were associated with a fourfold higher risk for adverse outcome.

In a study among 36 biomarkers, CRP was the most useful marker to identify an AECOPD[14].

CRP is an inflammatory marker which is inexpensive and can be measured for assessment of systemic inflammation. It is produced by the liver cells under transcriptional regulation by cytokines. Unlike cytokines, serum CRP levels remain quite stable in the same individual within 24 hours and reflect the level of inflammation[15,16].

De Torres et al[17] showed that serum CRP correlated with spirometric parameters and the severity of the disease according to the GOLD classification. However, in their study CRP levels were not associated with mortality in moderate-to-severe COPD patients[18].

CRP is a useful and sensitive indicator of bacterial infections. CRP is helpful for differentiating between bacterial pneumonia and meningitis from their viral counterparts[19].

There is increasing evidence that COPD is associated with chronic systemic inflammation. The use of biomarkers in the blood or breath condensate to predict the evolution of an AECOPD may allow earlier intervention.

In a study by Aaron et al[20], among several serum proteins only serum CRP, myeloperoxidase and VEGF were significantly associated with the severity of lung function impairment and dyspnea.

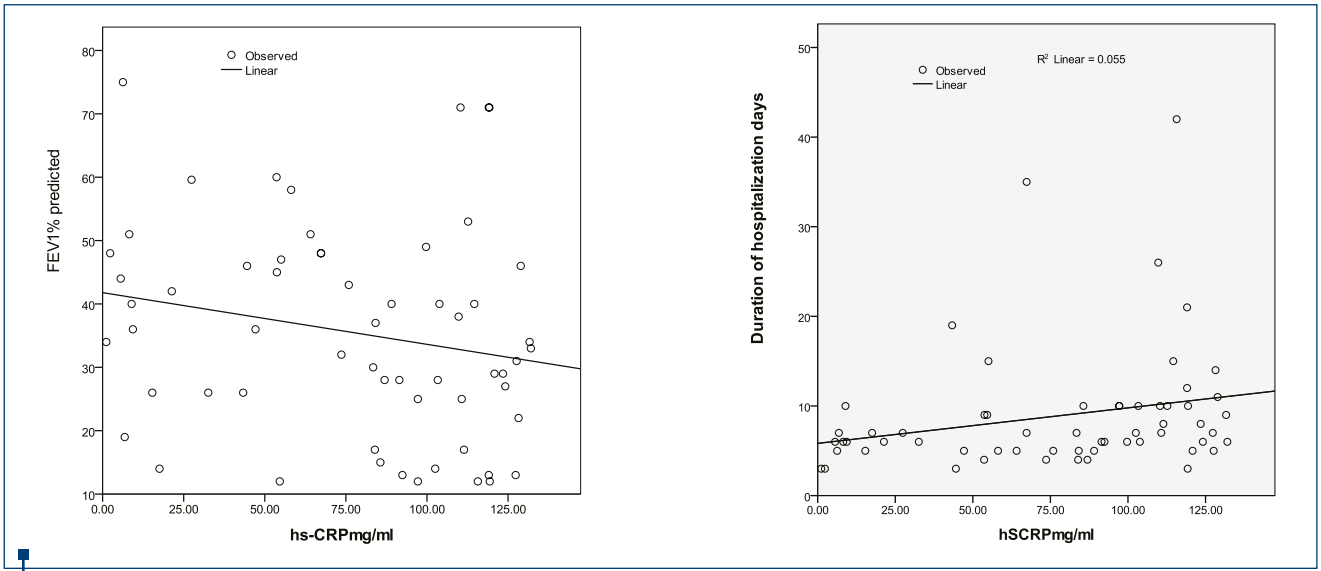

Figure 1. Serum hs-CRP level correlation with (A) FEV1 as percent of predicted and (B) duration of hospitalization (days)

AECOPD is s a very common cause of hospital admission and prediction of outcome during hospitalization is important. Another study showed that in-hospital mortality related to lower PaO_2, lower oxygen saturation, higher $PaC0_2$ and a longer hospital stay[11]. A study in more elderly patients with COPD reported that mortality is related to higher $PaC0_2$ and the long-term use of corticosteroids.

Ruiz-Gonzalez et al.[3] showed that high CRP level associated with higher mortality, need for ICU transfer, intubation or mechanical ventilation, congestive heart failure, mortality within 15 days after discharge.

Prediction of not only mortality but also the probability of complications is necessary for physicians. We studied variables other than mortality, such as the need for ICU transfer, intubation, mechanical ventilation, re-hospitalization or mortality within 30 days after discharge, and duration of hospitalization. This study found a positive linear relationship between hs-CRP levels and the duration of hospitalization and negative correlation with FEV1. Since in the present study hs-CRP was measured in frozen serum samples after discharge of the patient, the physicians were blinded to the hs-CRP levels and so this couldn't affect or biase physician's decision in patient's management during hospitalization.

Conclusion

The present study demonstrates that high serum levels of hs-CRP (≥ 100 mg/dl) significantly correlates with adverse outcome in patients hospitalized with AECOPD.

This article displays results of Dr F. Tofan, resident of internal medicine, thesis. ■

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