Prim Care Respir J 2011; **20**(4): 407-413

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

RESEARCH PAPER

Differences in local and systemic inflammatory markers in patients with obstructive airways disease

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Originally submitted 27th March 2010; resubmitted 16th December 2010; revised 13th April 2011; accepted 7th May 2011; online 2nd August 2011

Abstract

Background: Asthma and chronic obstructive pulmonary disease (COPD) are characterised by airway and systemic inflammation, but little is known about differences and similarities in inflammatory markers in patients with obstructive airways disease.

Methods: In 210 adult patients presenting to their general practitioners with symptoms suggestive of obstructive airways disease, lung function, fractional exhaled nitric oxide (FE_{NO}), blood eosinophils, and serum levels of high-sensitivity C-reactive protein (hs-CRP) and IgE were measured.

Results: hs-CRP levels were increased in COPD patients (p=0.009), whereas FE_{NO}, IgE, and eosinophils were increased in patients with asthma (p=0.009, p=0.041, and p=0.009, respectively). In the ROC analysis, hs-CRP had the largest area under the curve (AUC=0.651; 95% confidence interval (CI) 0.552 to 0.749), with a specifity of 83% and a sensitivity of 42% for the diagnosis of COPD. FE_{NO} was the most accurate marker in the diagnosis of asthma (AUC=0.618; 95% CI 0.529 to 0.706). Serum hs-CRP levels correlated with the number of smoking pack-years (r=0.218, p=0.001) and inversely with lung function parameters.

Conclusions: Levels of serum hs-CRP, IgE, blood eosinophils, and FE_{NO} identify distinct aspects of local and systemic inflammation in patients with obstructive airways disease. This might help to differentiate between asthma and COPD in primary care patients when spirometry is not available.

L Tilemann *et al*. *Prim Care Respir J* 2011; **20**(4): 407-413
http://dx.doi.org/10.4104/pcrj.2011.00069

Keywords asthma, COPD, diagnosis, inflammatory markers, local, systemic

See linked editorial by Thomas and Taylor on pg 349

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are increasingly important chronic airway diseases. The use of the patient history – including signs and symptoms, smoking status, and allergy presentation – may help to differentiate disease characteristics, as well as pulmonary function testing with an assessment of reversibility and bronchial hyperresponsiveness.[1] However, improvement in diagnostic accuracy is needed. The present approach in understanding and differentiating asthma and COPD is the use of inflammatory markers since both diseases are characterised by local and systemic inflammatory processes. As a marker of eosinophilic airway inflammation, fractional exhaled nitric oxide (FE_{NO}) is increased in patients with asthma.[2,3] Serum immunoglobulin E (IgE) levels are known to be associated with asthma,[4,5] and a significant increase in the number of peripheral blood eosinophils was found in patients with asthma that correlated with the clinical severity of asthma and pulmonary function.[6] Elevated levels of C-reactive protein (CRP) are established in COPD[7-9] but, in asthma, the results have been inconsistent. In recent studies high-sensitivity CRP concentrations (hs-CRP) were significantly higher in asthma patients than in controls without obstructive airways disease (OAD).[10,11] Other workers have reported that elevated levels of hs-CRP were associated with respiratory symptoms and non-allergic asthma but not with allergic asthma or bronchial hyperresponsiveness.[12] Higashimoto *et al*. investigated

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differences in systemic inflammation between asthma and COPD and found similar hs-CRP levels in asthma and COPD patients.[13] Significant differences in hs-CRP concentrations between OADs have not yet been reported.

There have been various attempts to predict the response to treatment by inflammatory markers[14-16] and to predict the progress of asthma or COPD.[17-20] However, similarities and differences in inflammatory patterns between asthma and COPD and the diagnostic accuracies of most inflammatory markers have not been determined. The aim of the present study was to evaluate differences in airway and systemic inflammatory markers among primary care patients with asthma, COPD, and partially reversible airway obstruction. This might assist the differentiation between asthma and COPD in primary care.

Methods

Study population and design

Two hundred and ten adults presenting to their general practitioners (GPs) for the first time with complaints suggestive of OAD were consecutively included. The patients had dyspnoea, coughing and/or expectoration persisting for at least 2 months. The GPs were advised to exclude subjects with respiratory tract infections in the six weeks prior to investigation. The other exclusion criteria included the well-known contraindications for bronchodilator reversibility testing or bronchial provocation – namely, pregnancy, untreated hyperthyroidism, unstable coronary artery disease, and cardiac arrhythmia.

Over a period of two weeks, subjects were referred to the lung function laboratory of the University Medical Hospital for further investigation. Structured medical histories were documented. All subjects underwent body plethysmography on the day of hs-CRP, IgE, blood eosinophil and FE_{NO} measurements. In 11 subjects (5.2%), anti-asthma treatment with inhaled corticosteroids had already been started by the referring GP because of severe airway obstruction. Patients were instructed not to use any bronchodilator or inhaled steroid and to stop smoking 12 hrs before visiting the lung function laboratory. The number of pack-years was calculated as years of smoking/20 x number of daily cigarettes. Subjects were categorised as never smokers if they had smoked less than 1 pack-year by the time of the study. Body mass index (BMI) was calculated as weight (kg)/square of height (m^2). The study was approved by the Medical Ethics Committee of the University of Heidelberg and all patients gave written consent.

Measurement of FE_{NO}, hs-CRP, IgE and eosinophils

Patients underwent measurement of FE_{NO} using a NioxMino® analyser (Aerocrine AG, Solna, Sweden) at a mouth flow rate of 50mL/s over 10s and a pressure of 10cmH_2O according to the guideline recommendation.[21] This procedure was performed at the lung function laboratory of the University Medical Hospital before investigation with body plethysmography and bronchial provocation as forced inspiratory and expiratory manoeuvres can lead to distorted FE_{NO} results.[22] Samples of peripheral venous blood were collected. Serum hs-CRP levels were measured with a high-sensitivity nephelometric assay (ADVIA® 2400 Hematology System, Siemens Healthcare Diagnostics, Deerfield, IL, USA) and IgE levels with an electro-chemiluminescence assay (Modular Analytics EVO solution, Roche Diagnostics, Switzerland). Eosinophil counts were performed with flow cytometry (ADVIA® 2120 Hematology System, Siemens Healthcare Diagnostics). Owing to technical difficulties, there were 13 missing values for eosinophils. In addition, 54 FE_{NO} measurements were missing as FE_{NO} was initially planned to be part of a diagnostic study only.[23]

Pulmonary function testing

All 210 subjects with respiratory symptoms suggestive of an OAD underwent body plethysmography in the lung function laboratory of the University Medical Hospital according to standard protocols.[24] Lung function reference values corrected for sex, age, and height were used.

Patients with forced expiratory volume in one second (FEV_1) <80% of predicted received a bronchodilation test with an additional whole body plethysmography 20 mins after inhaling 400µg salbutamol. An OAD was diagnosed if FEV_1/vital capacity (VC) was ≤0.7.

The obstruction was classified as irreversible (indicating COPD) if the postbronchodilator FEV_1 was less than 12% compared with baseline and was below 200mL. The obstruction was classified as fully reversible (indicating 'asthma') if the degree of reversibiliy in FEV_1 was >12% and >200mL from baseline and lung volumes returned to the predicted normal range. An incomplete bronchodilator response (indicating partial reversibility) was considered to be present if the bronchodilation response was >12% and >200mL compared with baseline but lung volumes remained below the predicted levels.

If there was no obstruction in the first lung function test, a bronchial provocation test with methacholine was performed according to the American Thoracic Society guidelines to determine bronchial hyperresponsiveness.[25] Asthma was diagnosed if there was a fall of >20% in FEV_1 after inhaling methacholine stepwise up to the maximum concentration (PC_{20} ≤16mg/mL).

Statistical analysis

The data were analysed with SPSS 15.0 for Windows. Baseline data are presented as median or mean±SD. The Mann-Whitney U test was used to analyse differences between the two groups and correlations were analysed using Spearman's rank correlation test; p values <0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were plotted, which allowed a graphical representation of sensitivity and specificity. The

corresponding areas under the curve (AUC) were calculated to estimate the diagnostic accuracy of each inflammatory marker. The AUC can range from 0.5 (model discrimination no better than by chance) to 1.0 (perfect model discrimination). Boxplots were constructed to illustrate the dispersion of each inflammatory marker by diagnosis. Cut-off values were determinated by identifying the concentration of the respective marker with the highest sum of sensitivity and specifity. hs-CRP values were divided into quartiles from the lowest to the highest levels for further analysis.

In some cases, asthma and COPD could hardly be differentiated. Repeated measurements after trials of medication were required, particularly to identify asthma with fixed obstruction. As long-term follow-up was not possible for organisational reasons, we performed an additional analysis in which never-smoking subjects with an incomplete or negative bronchodilation test were labelled as asthma patients.

Results

Characteristics and inflammatory patterns

Patients with COPD (n=36) were significantly older (p<0.001), had accumulated more pack-years (p<0.001), and had lower lung function parameters than patients with asthma (n=86) and those with no OAD (n=75). The characteristics of COPD patients were similar to those of patients with partial reversibility of airflow obstruction (n=13; Table 1). Patients with asthma differed in age (p<0.001), number of pack-years (p<0.001), and lung function parameters from those with partial reversibility. The BMI of asthma patients was lower than that of COPD patients.

COPD patients had significantly higher levels of hs-CRP than asthma patients (p=0.003) and subjects with no OAD (p=0.018; Table 2). There were no significant differences in any of the inflammatory markers between COPD patients and patients with partial reversibility of airflow obstruction. Asthma patients had higher levels of FE_{NO}, IgE, and blood eosinophils than COPD patients (p=0.004, p=0.013, and p=0.007, respectively). Between asthma patients and those with partial reversibility of airflow obstruction, there was a difference in FE_{NO} concentrations but not in hs-CRP and IgE levels or eosinophils. Even though the differences in inflammatory markers between asthma patients and those with COPD were significant, the box plots indicated a substantial degree of overlap in the inflammatory markers by diagnosis (Figure 1).

In an additional analysis, six never-smoking subjects without reversibility of airflow obstruction and two never-smoking subjects with partial reversibility of airflow obstruction were redefined as having asthma (with fixed obstruction). The significance levels of differences in levels of inflammatory markers between asthma and COPD remained unaltered for hs-CRP (p=0.003), increased for FE_{NO} (p=0.002), and decreased for IgE (p=0.023) and eosinophils (p=0.039; not shown).

There were no significant differences between male and female patients in inflammatory markers except for IgE

Table 1. Descriptive characterisation of patients with asthma, COPD, partial reversibility, and no OAD

	Asthma (n = 86)	COPD (n = 36)	Partial reversibility (n = 13)	No OAD (n = 75)
Age (yrs), mean ± SD	38.0 ± 14.6**/§§	56.8 ± 11.7	57.9 ± 11.2	42.3 ± 14.4**/§§
Person-years (n), mean ± SD	6.4 ± 12.9**/§§	31.2 ± 23.1	21.8 ± 17.0	6.7 ± 12.2**/§§
Smoking status, n (%)				
Current smokers	17 (19.8)	17 (47.2)	8 (61.5)	21 (28.0)
Past smokers	11 (12.8)	13 (36.1)	3 (23.1)	9 (12.0)
Never smokers	58 (67.4)	6 (16.7)	2 (15.4)	45 (60.0)
Male, n (%)	31 (36.0)	17 (47.2)	7 (53.8)	31 (41.3)
BMI (kg/m^2), mean ± SD	24.5 ± 4.0*	26.6 ± 4.1	26.3 ± 4.5	25.6 ± 4.8
Pulmonary function, mean ± SD				
VC, % predicted	105.4 ± 11.5**/§§	90.7 ± 17.7	92.7 ± 18.2	107.8 ± 13.5**/§§
FEV_1, % predicted	99.7 ± 12.0**/§§	69.1 ± 17.1	67.6 ± 17.2	106.3 ± 12.8**/§§
FEV_1/VC, %	78.2 ± 7.2**/§§	59.9 ± 9.0	57.5 ± 8.7	81.0 ± 6.0**/§§
ITGV, % predicted	119.8 ± 24.0**/§	140.2 ± 29.5	145.6 ± 29.5	118.7 ± 18.8**/§
RV, % predicted	125.0 ± 24.3**/§§	166.1 ± 46.0	171.2 ± 44.4	121.6 ± 27.6**/§§
MEF_{25}, % predicted	79.8 ± 20.8**/§§	31.5 ± 12.1	28.8 ± 11.4	93.3 ± 25.4**/§§
MEF_{50}, % predicted	66.9. ± 22.7**/§§	23.8 ± 9.0	23.0 ± 10.1	78.5 ± 28.4**/§§

*p<0.01 compared with COPD; **p<0.001 compared with COPD; §p<0.01 compared with partial reversibility; §§p<0.001 compared with partial reversibility.

BMI=body mass index; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in one second; ITGV=intrathoracic gas volume; MEF_{25}=maximum expiratory flow rate at 25% of vital capacity; MEF_{50}=maximum expiratory flow rate at 50% of vital capacity; OAD=obstructive airways disease; RV=residual volume; VC=vital capacity.

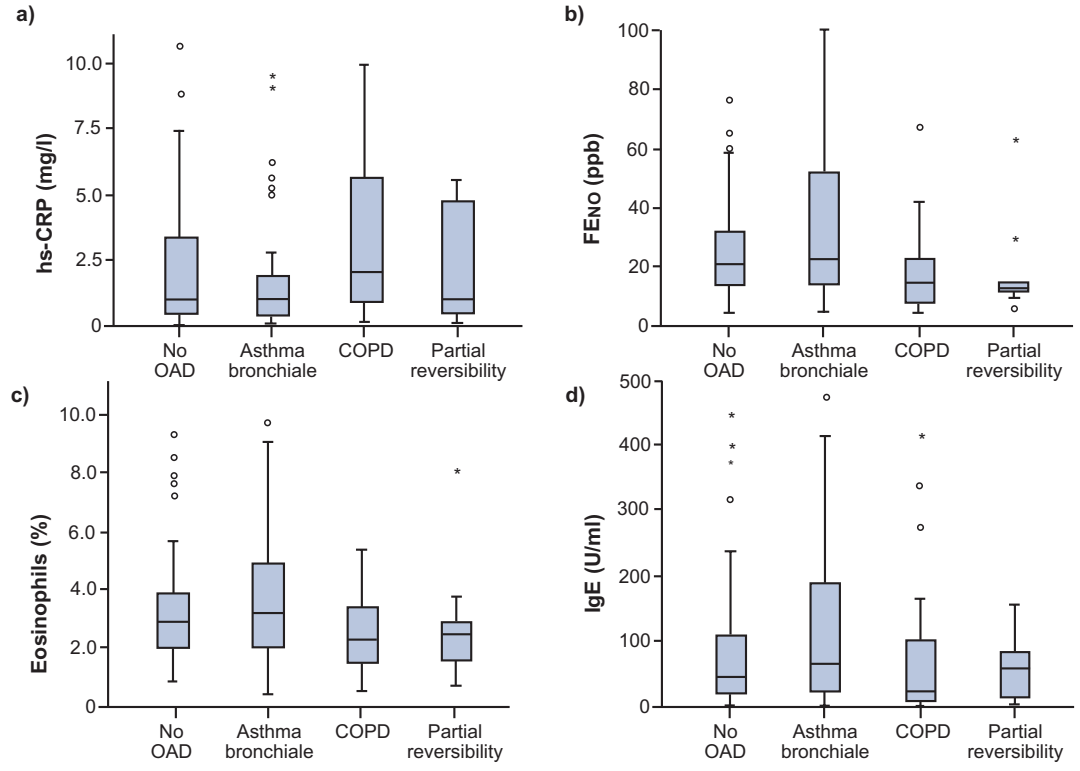
Table 2. Inflammatory markers in asthma, COPD, partial reversibility, and no OAD

	Asthma	COPD	Partial reversibility	No OAD
hs-CRP (mg/L)				
Mean±SD (95% CI of mean)	1.9 ± 3.1** (1.2 to 2.6)	4.7 ± 7.2 (2.2 to 7.1)	5.6 ± 11.0 (0.0 to 12.3)	2.3 ± 2.7* (1.7 to 2.9)
Median	1.0	2.0	1.0	1.0
FE_{NO} (ppb)				
Mean±SD (95% CI of mean)	40.1 ± 46.9**/§ (29.1 to 51.1)	18.5 ± 14.7 (12.5 to 24.5)	19.6 ± 17.6 (6.1 to 33.1)	25.3 ± 16.4* (20.6 to 30.0)
Median	23.0	14.5	13.0	21.0
Eosinophils (%)				
Mean±SD (95% CI of mean)	4.0 ± 3.1** (3.3 to 4.7)	2.6 ± 1.4 (2.1 to 3.1)	2.8 ± 1.8 (1.7 to 3.9)	3.2 ± 1.8 (2.8 to 3.6)
Median	3.2	2.3	2.8	3.0
IgE (U/mL)				
Mean±SD (95% CI of mean)	173.2 ± 266.4* (116.1 to 230.3)	80.4 ± 113.1 (42.1 to 118.7)	131.0 ± 262.6 (0.0 to 289.7)	129.9 ± 242.3 (74.2 to 185.6)
Median	67.2	27.0	59.9	47.0

*p<0.05 compared with COPD; **p<0.01 compared with COPD; §p<0.05 compared with partial reversibility.

CI=confidence interval; COPD=chronic obstructive pulmonary disease; FE_{NO}=fractional expired nitric oxide; hs-CRP=high-sensitivity C-reactive protein; OAD=obstructive airways disease; SD=standard deviation.

Figure 1. Box plots illustrating the distribution of (a) high-sensitivity C-reactive protein (hs-CRP), (b) fractional exhaled nitric oxide (FE_{NO}), (c) eosinophils and (d) IgE within the diagnostic groups. Boxes represent the median and interquartile range (IQR); whiskers represent observations <1.5 IQR outside the central box. Open circles represent outliers and asterisks represent extreme outliers



(p=0.004). FE_{NO} concentrations and eosinophils were higher in current non-smokers (never smokers and ex-smokers) than in current smokers (p<0.001 and p=0.015, respectively). In contrast, there were no significant differences in hs-CRP and IgE concentrations between current smokers and non-current smokers.

The ROC curves illustrate the diagnostic accuracy of each inflammatory marker (Figure 2). The AUC was highest for

Figure 2. ROC curves illustrating the accuracy of (a) high-sensitivity C-reactive protein (hs-CRP) (AUC=0.651; 95% CI 0.552 to 0.749) in the diagnosis of chronic obstructive pulmonary disease COPD and the accuracy of (b) fractional exhaled nitric oxide (FE_{NO}) (AUC=0.618; 95% CI 0.529 to 0.706), (c) eosinophils (AUC=0.602; 95% CI 0.520 to 0.683), and (d) IgE (AUC=0.584; 95% CI 0.505 to 0.663) in the diagnosis of asthma

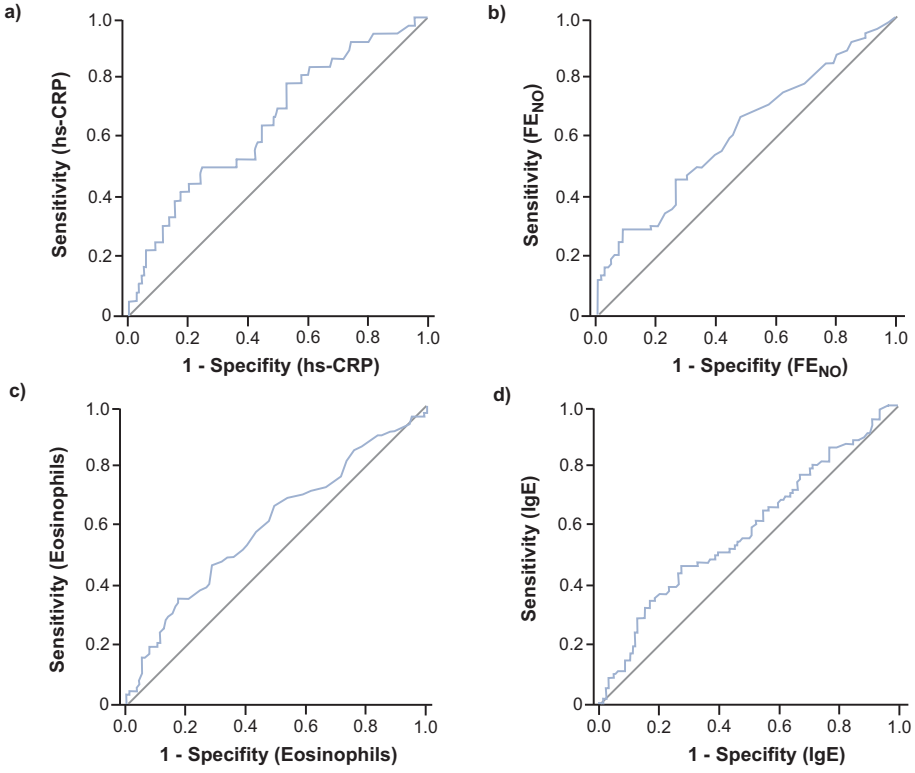


Table 3. Relation between hs-CRP, smoking history, BMI, and lung function parameters

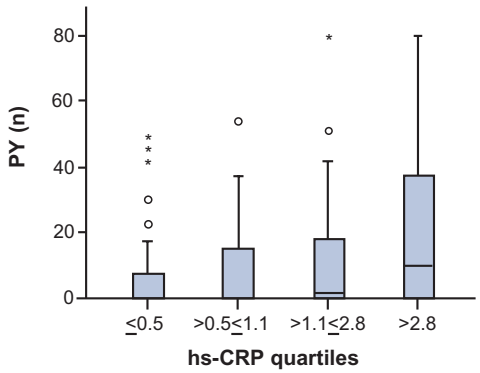
hs-CRP (mg/L)*	n	Pack-years (n) Mean ± SD	BMI (kg/m²) Mean ± SD	VC pred (%) Mean ± SD	FEV_1 pred (%) Mean ± SD	FEV_1/VC (%) Mean ± SD	MEF_{50} pred (%) Mean ± SD	MEF_{25} pred (%) Mean ± SD
≤0.5	54	6.4 ± 12.1	22.4 ± 2.5	103.6 ± 15.1	97.3 ± 18.8	77.2 ± 10.9	79.6 ± 32.8	70.9 ± 32.7
>0.5 ≤ 1.115	51	8.4 ± 13.4	24.9 ± 3.5	103.8 ± 16.3	96.9 ± 22.3	75.4 ± 12.2	75.0 ± 33.9	64.6 ± 32.1
>1.115 ≤ 2.8	54	11.7 ± 17.2	26.3 ± 3.9	104.5 ± 12.9	96.4 ± 16.5	74.7 ± 09.8	73.5 ± 27.3	57.8 ± 23.0
>2.8	51	20.6 ± 23.7	28.0 ± 5.2	99.8 ± 16.5	88.4 ± 21.4	71.6 ± 11.9	64.2 ± 32.6	50.1 ± 32.8
p value		0.001	<0.001	0.099	0.006	0.002	0.007	<0.001

hs-CRP concentrations were categorised in quartiles.

BMI=body mass index; FEV_1=forced expiratory volume in one second; hs-CRP=high-sensitivity C-reactive protein; MEF_{25}=maximum expiratory flow rate at 25% of vital capacity; MEF_{50}=maximum expiratory flow rate at 50% of vital capacity; pred=predicted; VC=vital capacity.

hs-CRP in the diagnosis of COPD (AUC=0.651; 95% CI 0.552 to 0.749). The best cut-off values to discriminate between COPD and no COPD were hs-CRP concentrations of 2.39mg/L and 3.5mg/L. The lower cut-off at 2.39mg/L resulted in a specificity of 75%, sensitivity of 50%, negative predictive value (NPV) of 88% and positive predictive value (PPV) of 30%. At a concentration of 3.5mg/L the specificity was 83%, sensitivity was 42%, NPV was 87%, and PPV was 33%. FENO was the best marker in the diagnosis of bronchial asthma (AUC=0.618; 95% CI 0.529 to 0.706), and the optimal cut-off at 46ppb had a specificity of 92%, sensitivity of 29%, PPV of 71%, and NPV of 65%. The AUC for blood eosinophils was 0.602 (95% CI 0.520 to 0.683). The optimal cut-off was at 4.15% with a specificity of 83%, sensitivity of 36%, PPV of 59%, and NPV of 65%. IgE had the smallest AUC (AUC=0.584 (95% CI 0.505 to 0.663). The optimal cut-off was at 90U/mL with a specificity of 73%, sensitivity of 47%, PPV of 54%, and NPV of 66%. The ROC curves showed that hs-CRP and FE_{NO} in particular had some ability to discriminate patients. Nonetheless, the runs of the ROC curves also

Figure 3. Relation between the concentration of high-sensitivity C-reactive protein (hs-CRP) and the number of pack-years (PY). Boxes represent median and interquartile range (IQR); whiskers represent observations <1.5 IQR outside the central box. Open circles represent outliers and asterisks represent extreme outliers



suggested that there was a large overlap between the measures by diagnosis.

Correlations between hs-CRP, smoking history, lung function parameters and BMI

hs-CRP concentrations were related to smoking history, lung function parameters, and BMI (Table 3). There was a significant correlation between hs-CRP levels and the number of pack-years (p=0.001, r=0.218, Figure 3). When the analysis was restricted to patients with OAD (asthma, COPD, and partial reversibility of airflow obstruction), the correlation coefficient increased (p<0.001, r=0.304). There was no significant association between hs-CRP levels and the number of pack-years in subjects without OAD (not shown). hs-CRP levels correlated positively with BMI (p<0.001, r=0.474) and negatively with FEV_1 (p=0.006, r=–0.190) and FEV_1/VC (p=0.002, r=–0.213).

Correlations between hs-CRP, FE_{NO}, IgE and eosinophils

There were correlations between blood eosinophils and IgE levels (p<0.001, r=0.266), between blood eosinophils and FE_{NO} concentrations (p<0.001, r=0.284), and between FE_{NO} and IgE levels (p<0.001, r=0.280). There were no significant correlations between the hs-CRP concentration and the levels of any of the other investigated inflammatory markers.

Discussion

The major finding of the present study is that there are distinctive inflammatory profiles in patients with asthma compared with COPD patients, thereby identifying different aspects of inflammation in OAD. Overall, hs-CRP had the highest diagnostic accuracy. In the diagnosis of asthma, FE_{NO} was superior to IgE and blood eosinophils. Nevertheless, there was some overlap between the inflammatory markers by diagnosis.

Low-level inflammation, as indicated by increased hs-CRP serum concentrations, has been described in both COPD[7-9] and asthma.[10,11] However, only one recent study has investigated differences in hs-CRP levels between patients with COPD and those with asthma. Higashimoto *et al*. compared systemic inflammatory markers in patients with OAD and did not find a significant difference in hs-CRP concentrations between asthma and COPD patients.[13] This is in contrast to the present findings of significantly increased hs-CRP levels in COPD patients. However, there are differences in the patients studied. In the present study, subjects mainly presented in the early stages of disease and only 11 patients were already receiving steroids. In contrast, Higashimoto *et al*. provided no information about the duration of disease and the current medication and, moreover, there were few lifetime non-smokers.

Significant differences in hs-CRP levels between subjects with severe asthma and controls without any respiratory symptoms have recently been demonstrated.[10] In contrast, in a study by Takemura *et al*., hs-CRP levels were only increased in steroid-naive patients compared with controls.[11] In our study the difference between asthma patients and without OAD (but with persistent respiratory symptoms) was not statistically significant; hs-CRP levels in both groups were very low.

In the present study there were six never-smoking patients without reversibility of airflow obstruction and 13 subjects with partial reversibility of airflow obstruction. A trial of inhaled steroids might have been helpful to differentiate between asthma and COPD in these patients. However, this was not the focus of the present study design with only a single lung function test. In an additional analysis the six never-smoking patients without reversibility of airflow obstruction and two never-smoking subjects with partial reversibility of airflow obstruction were labelled as asthma, although the significance levels of differences in inflammatory marker concentrations between asthma and COPD did not change to a great extent.

Data on inflammatory markers in patients with partial reversibility of airflow obstruction are currently scare.[26,27] According to Papi *et al*., FE_{NO} levels were higher in patients with partial reversibility (in their study defined as an increase in FEV_1 of <12% but >200mL after 200µg inhaled salbutamol) than in those with no reversibility of airflow limitation.[26] In a study by Fabbri *et al*., subjects with fixed airway obstruction and a history of asthma had more eosinophils in the peripheral blood and higher FE_{NO} levels than subjects with a history of COPD.[27] In the present study the characteristics and inflammatory patterns of subjects with partial reversibility of airflow obstruction were similar to those of COPD patients. However, the differences in inflammatory patterns between patients with asthma and those with partial reversibility of airflow obstruction were not

significant, except for FE_{NO}. This might be due to the small number of patients with partial reversibility of airflow obstruction in the study. Moreover, we are aware of the limitation of a single lung function test to determine a final diagnosis, as a negative or partial bronchodilator response can be due to fixed airway obstruction in asthma. Further studies are required to investigate the impact of inflammatory markers on the response to specific treatment, long-term management and outcome, particularly in this uncertain diagnostic group.

In all diagnostic groups there were numerous active smokers. The number of pack-years was positively correlated with hs-CRP levels. Thus, smoking history may influence the levels of inflammatory markers. The correlation was even stronger when the analysis was restricted to subjects with OAD. However, there was no significant association between the number of pack-years and hs-CRP concentrations in subjects without OAD. It might be speculated that subjects with OAD are more likely to develop systemic low-level inflammation after tobacco exposure. Nevertheless, little is known about the reasons why some smokers develop chronic airway disease whereas others do not. In a cross-sectional survey, active smoking was associated with increased odds of elevated CRP levels.[28] One group found a difference in hs-CRP concentrations between ex-smokers and current smokers[13] whereas others did not.[29] Also, in a recent epidemiological study, CRP levels did not vary by smoking status.[30] In the present study there were also no significant differences in hs-CRP concentrations between current smokers and non-current smokers. Overall, the accumulated pack years might have a higher impact on hs-CRP levels than current smoking status.

In conclusion, the results of the present study indicate that there are significant differences in inflammatory patterns between asthma and COPD. hs-CRP concentrations were increased in COPD patients, whereas blood eosinophils, FE_{NO}, and IgE levels were increased in patients with asthma. hs-CRP and FE_{NO} had the highest ability to discriminate between patients with asthma and COPD.

While the use of FE_{NO} in the diagnosis of asthma seems to be about to find its way into daily practice, the other inflammatory markers still attract little attention. To date, mainly lung specialists have started to integrate FE_{NO} measurements into their daily work but it is not generally used in primary care. Economic evaluations suggest that FE_{NO} might be a cost-effective tool for diagnosing and monitoring asthma,[31] so its more widespread use in primary care is feasible, when further studies can demonstrate diagnostic efficacy.

Currently, CRP is usually only determined if an exacerbation of COPD is suspected. Our data suggest that hs-CRP could be useful in differentiating between asthma and COPD. However, spirometry is already very efficient in the diagnosis of COPD and any added value of determining hs-CRP has not yet been demonstrated. Routine measurements of hs-CRP, IgE, and blood eosinophils for the diagnosis of asthma and COPD in a primary care setting would be useful only if they could also provide information about the response to treatment or disease progression.

Handling editor
Onno van Schayck

Statistical review
Gopal Netuveli

Conflicts of interest
The authors declare that they have no conflicts of interest in relation to this article.

Contributorship
All authors contributed to the realisation of this study and the preparation of the manuscript. In detail, LT analysed the data and wrote the manuscript. AS designed the study, helped analysing the data and writing the manuscript. LG was assistant investigator and helped gaining the data. FM interpreted the lung function testing and helped with writing. JS supported implementing the study.

Funding
The trial was funded by the Federal Ministry of Education and Research (BMBF), Germany, grant no. 01GK0515. The funding source had no involvement in the design, collection, analysis or interpretation of the data.

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