Biomarkers in COPD – Challenging, Real or Illusive

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INTRODUCTION
Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation. It is associated with airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. The airflow limitation in COPD is caused by a mixture of small airways disease, and parenchymal destruction, the relative contributions of which vary from person to person. It is associated with complex gene-environment interaction. COPD is represented by an abnormal inflammatory response to noxious stimuli and is linked to a range of pathological changes, such as mucus hypersecretion and airway obstruction. Inflammatory cell infiltrate is primarily represented by neutrophils, cytotoxic CD8-T-cells, macrophages and sometimes eosinophils that produce a huge amount of cytokines, chemokines, enzymes and mediators, giving quite heterogeneous clinical presentation and course of the disease. The new concepts of phenotyping and clustering patients triggers the generation of biomarkers. They are any clinical features, imaging data or laboratory-based tests that characterise disease. According to the definition of the National Institute of Health, a biomarker is a “characteristic that is objectively measured and evaluated as an indicator of normal or pathogenic processes, or reflects pharmacologic response to a therapeutic intervention”. Biomarkers may either reflect the impairment that is already present, the process that has led to this impairment or the counter reaction of the organism to it. By the definition above they are also indicative for the effectiveness of therapy or for the progression of the disease. The new technological approaches of the “omics” are generating an over flow of biomarkers, facilitating the clustering of patients according to molecular and genetic expression profiles, rather than producing clinically based systematic classification. The production of confusing biomarkers in this field stems from the fact that COPD has different phenotypes that cannot be put in the ramification of GOLD (Global Obstructive Lung Disease) stages. On the other hand, this kind of research is mainly basic science and abrogates clinical benefit if any.
The present review summarizes the current concepts of biomarker development in COPD, the problems and future in this field of respiratory medicine.

CURRENT CLINICAL MARKERS

SIGNS, SYMPTOMS, COMPOSITE SCORES

The ‘gold standard’ biomarker to date is still the objective measurement of lung physiology. Forced expired volume in 1 second (FEV₁) is a paramount description of COPD severity. It is a marker of disease progression and response to therapy, as well as mortality. However, it reflects one aspect of COPD, poorly correlates with the extent of lung parenchyma destruction, disease progression, or patients’ quality of life. The ‘comorbidome’, the presence of comorbidities, and the new paradigm assuming COPD as a multisystemic disease has led to a new approach that tries to assess COPD patient’s health status. The degree of breathlessness, exercise limitation, and low BMI (body-mass-index), patient’s health status. The degree of breathlessness, exercise limitation, and low BMI (body-mass-index), for example, are associated with mortality, but they characterize health status only scarcely. Although predicting one and the same - long-term mortality, they do not necessarily reflect one and the same thing. To overcome this, composite scores for health status have been introduced into clinical practice, such as the BODE index (Body mass index, airflow Obstruction, Dyspnoea and Exercise), mBODE (BODE modified in grading of walked distance), ADO (Age, Dyspnoea, airflow Obstruction), DOSE (Dyspnoea, Obstruction, Smoking, Exacerbation). Composite scores have been created to characterize disease activity, severity and its impact on health status and prognosis. Although not predictive of progression per se, they are useful as measures of cohort risk. Unfortunately, they are less specific in assessing the individual patient and the progression of his health status.

PATIENT SYMPTOMS

Despite being very subjective, symptoms are included in many outcomes. They are scored as indicators of disease progression, response to treatment, as well as impact on individual health status. Different tests based on patients’ symptoms have been applied. COPD Assessment Test (CAT), is at present the most recent questionnaire that has been applied in practice. CAT confirms the weak relationship between spirometry and disease state. Its validation is based on the comparison with other patient-reported outcomes. Despite this, subjective questionnaires are still biomarkers of the impact of the disease on the patient, even if this is not entirely explained by the current objective measures (spirometry).

IMAGE BIOMARKERS

Radiological features of COPD morphology on high resolution computed tomography (CT) chest scan are useful predictors of disease progression, exacerbations and mortality. High resolution-CT assesses emphysema and airway disease using quantitative indices.

Airway wall thickness. Airway wall thickness is usually met in more symptomatic smokers and is associated with reduced lung function in a cross-sectional study. In the COPDGene study frequent exacerbators displayed increased airway wall thickness. It is not, however, independently associated with mortality.

Emphysema. CT provides the division of COPD patients into phenotypes. Inspiratory vs. expiratory scans reveal distribution of emphysema. The follow-up of lung density can itself be an endpoint of COPD progression. Quantitative CT indices have been confirmed as markers of outcomes and COPD progression in large cohort studies. More severe emphysema, measured, quantitatively by CT, correlates with accelerated decline in lung function. The MESA (Multi-Ethnic Study of Atherosclerosis) study found that centrilobular and panlobular emphysema correlate with increased dyspnoea and reduced exercise capacity. In the COPDGene study of 1002 subjects, a higher CT emphysema index increases the risk of exacerbations respiratory and COPD-specific mortality.

Bronchiectasis. Bronchiectasis often coexist in COPD. In some patients, they are subclinical, an incidental CT finding, as in others they provoke frequent exacerbations. The overall prevalence of bronchiectasis in milder COPD patients, according to the ECLIPSE study, is 4%. In moderate-to-severe COPD a higher prevalence of 30% to 60% may be found. The presence of bronchiectasis influences respiratory infections and other complications of COPD. Their coexistence in COPD causes more severe airflow obstruction (OR 3.9) and an increased rate of exacerbations (OR 3.0). A Belgian study of 245 patients with non-cystic fibrosis bronchiectasis showed that 17% of patients had co-existing COPD. Those with both bronchiectasis and COPD had a five-year mortality rate of 55%, which was considerably higher than patients with bronchiectasis alone - 13%. In a study of 201 patients with

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moderate-to-severe COPD, bronchiectasis were also independently associated with increased all-cause mortality (HR 2.5). 17

**Coronary artery calcification (CAC).** Coronary artery calcification (CAC) is a marker of atherosclerosis. A high prevalence of coronary artery disease has been associated with emphysema severity. Using routine CT chest in a cross-sectional study of 200 COPD patients with moderate to severe COPD, a high prevalence of CAC (87%) was found. 18 Visual score for CAC >4 was predictive of increased all-cause mortality (HR 2.0), which is independent of Brinkman index. Similar data are reported in the ECLIPSE study in which a higher coronary artery calcium score percentile was associated with increased risk of all-cause mortality (HR 2.5). 17

**PATHOBIOLOGY AND MOLECULAR PATHOGENESIS**

Though useful, the clinical biomarkers have been overtaken by biological biomarkers and the term ‘biomarker’ has been associated with a fluid sample test that is specific, particularly in terms of the pathophysiological processes taking place.

**LUNG TISSUE: GENE EXPRESSION MARKERS**

Molecular changes in lung tissue are a direct reflection of the complex immunopathology of COPD. Gene expression analysis provides a valuable insight into biomarker research. Seven genes were reported to be differentially expressed in moderate and mild emphysema by gene expression profiling. Results were confirmed by PCR. 20 Similar results are reported in another study of lung tissue from patients with mild (n=9) or moderate (n=9) COPD. Differential expression of eight genes was detected and validated in 58 samples. 21 Expression of repair genes was compared in 136 paired small airways and emphysema lung tissue obtained by laser capture microdissection from 63 patients. Genes responsible for tissue destruction were increased in emphysematous lung tissue and correlated with impaired FEV1. Patients with combined pulmonary fibrosis and emphysema were also subjected to gene expression analysis. 22 Different gene signatures in fibrotic and emphysematous areas of lung were found. Emphysematous regions presented with genes involved in cellular fraction, membrane biology, and vascular biology. Fibrotic regions expressed genes responsible for immunity. Global mRNA expression has been applied to characterize the different severity stages of COPD. Lung tissue samples from COPD patients were obtained. Results show that gene expression profiles correlated with forced expiratory flow 25% -75% (FEF25-75%). 23 Upregulated genes were responsible for apoptosis, extracellular matrix synthesis and degradation; anti-inflammatory genes were down-regulated.

**LUNG TISSUE: PROTEIN MARKERS – THE PROTEASE/ANTIPROTEASE HYPOTHESIS**

The long standing theories regarding the imbalance between proteases and antiproteases implicate the idea to look for biomarkers that can assess protease activity or the degradation products that are released during the process. None of the approaches, however, comes to reality. Elastase is difficult to measure. It is rapidly inhibited from local antiproteases, even if bound to elastin. The degradation products of elastin - desmosine and isodesmosine are not lung specific, because elastin is a component of extracellular matrix elsewhere. The release of elastase from activated neutrophils within the lung tissues is necessary to cause the proteolytic damage. In sputum, elastase is measurable in case of neutrophilic exacerbations and is unreliable, because it is also met in patients with bronchiectasis (cystic and non-cystic). 24, 25 To overcome this, bronchoalveolar lavage (BAL) has been analysed. The invasiveness of the procedure, the lack of standard interpretation, are major drawbacks, thus BAL has contributed little to biomarker research. An alternative approach to the detection of lung elastase activity has been developed. The neutrophil elastase is active in a certain area in the lung for a limited time period. The cleavage of the surrounding structures is a biochemical proof of enzyme activity. A specific proteolytic product of fibrinogen (Aα-Val360) has been attributed to lung physiology. The biomarker is reproducible and decreases with augmentation therapy in alpha-1 antitrypsin deficiency (AATD). Concentrations were higher in COPD. 26 They correspond to spirometric and radiological indexes of emphysema. It seems that neutrophil elastases are of key importance, as they indirectly activate other proteolytic enzymes - cathepsin B, matrix metalloproteinases (MMPs), tumor necrosis factor (TNF)-α. Leeming et al. have also investigated blood markers of disease progression. They included 1000 COPD patients that participated in the ECLIPSE study. Baseline values of FEV1, and their change were measured every six months during the two-year period of the study. Serum levels of MMP-mediated degradation of collagen type I and type VI have been correlated with increased mortality (HR 1.77). 19

**Coronary artery calciﬁcation** (CAC) and inflammation

Calcium score percentile was associated with increased all-cause mortality (HR 2.0), which is independent of Brinkman index. Similar data are reported in the ECLIPSE study in which a higher coronary artery calcification (CAC) is a marker of atherosclerosis. A high prevalence of coronary artery disease has been associated with emphysema severity. Using routine CT chest in a cross-sectional study of 200 COPD patients with moderate to severe COPD, a high prevalence of CAC (87%) was found. Visual score for CAC >4 was predictive of increased all-cause mortality (HR 2.0), which is independent of Brinkman index. Similar data are reported in the ECLIPSE study in which a higher coronary artery calcium score percentile was associated with increased mortality (HR 2.5). 17
also been determined at 6 months. The authors established that serum levels of collagen turnover markers have been independent predictors of disease progression, even after adjusting for sex, age, BMI, smoking, bronchodilator reversibility, prior exacerbations, emphysema and chronic bronchitis status. Bronchodilator reversibility, plasma hsCRP and emphysema were also significant predictors for FEV\textsubscript{1} change.\textsuperscript{27}

**BLOOD BIOMARKERS**

**Inflammatory markers as predictors of lung function**

Low levels of vitamin D correlated with FEV\textsubscript{1} and physical activity measured by the 6-minute walking distance test. They were also related to reduced bronchodilator response, emphysema severity and lower IL-16 plasma levels.\textsuperscript{28} Predictors of more severe emphysema are also lower levels of soluble receptor for advanced glycation endproducts (sRAGE). This was confirmed in two large studies - TESRA (Treatment of Emphysema with a Selective Retinoid Agonist) and ECLIPSE studies and two smaller ones.\textsuperscript{29} In the COPDGene cohort, lower levels of IL-16 and higher plasma levels of adiponectin related to emphysema quantified on CT.\textsuperscript{30} Reduced levels of club (Clara) cell protein 16 (CC-16) corresponded to accelerated lung function decline (FEV\textsubscript{1}) in the Lung Health Study and ECLIPSE study.\textsuperscript{30,31} Plasma proteins, functionally associated with neutrophils related to FEV\textsubscript{1}.\textsuperscript{32} Proteins of epidermal growth factor receptor (EGFR) signalling pathway related to gas transfer (DLCO) and FEV\textsubscript{1} in COPD patients.

Dicker et al. tried to determine whether neutrophil extracellular traps (NETs) are associated with disease severity in patients with COPD and how they are associated with microbiota composition and airway neutrophil function. Neutrophil biomarkers were measured in soluble sputum and serum from patients with COPD during disease stability and exacerbations. Sputum NET complexes were associated with the severity of COPD. This was stated, assuming the higher levels of NET complexes in patients with frequent exacerbations and the presence of modest correlation between NET complexes, FEV\textsubscript{1} and symptoms, evaluated by COPD assessment test. An association between NET complexes and microbiota diversity was detected. Patients with increased sputum NET complexes had suppressed airway neutrophil phagocytosis. Consistent results were observed regardless of the method of quantifying sputum NETs. NET formation is increased in patients with severe COPD and associated with more frequent exacerbations and a loss of microbiota diversity.\textsuperscript{33}

Zemans et al. hypothesized that multiple biomarkers may be more informative than individual biomarkers to predict subtypes, disease severity, disease progression, and mortality. A total of 1465 subjects from the COPDGene cohort and 2746 subjects from the ECLIPSE cohort were investigated. Plasma levels of fibrinogen, C-reactive Protein (CRP), surfactant protein D (SP-D), soluble receptor for advanced glycation endproducts (sRAGE), and club cell secretory protein (CC16) were measured. After adjustment for clinical covariates, a regression analysis was performed to detect if individual biomarkers, or a combination of them, may be predictive of subtypes, disease severity, progression and mortality. In the COPDGene study - CC16, sRAGE, fibrinogen, CRP, and SP-D were associated with airflow limitation; sRAGE, fibrinogen, CRP, and SP-D with emphysema; CC16, fibrinogen, and sRAGE were predictive for FEV\textsubscript{1} decline and emphysema progression. The combination of all biomarkers was predictive for mortality. Except for mortality all the data was also validated in ECLIPSE study. The combination of SP-D, CRP, and fibrinogen was the best combination for mortality prediction in ECLIPSE study. Authors proved that combinations of biomarkers improve predictive value compared with clinical variables and individual biomarkers.\textsuperscript{34} Bradford et al. used panels of 9 cytokines and chemokines in 2123 subjects from the COPDGene study and 1117 subjects from SPIROMICS to stratify high risk chronic obstructive pulmonary disease (COPD) patients. They explored the levels of interleukin IL-2, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, eotaxin/CCL-11, eotaxin-3/CCL-26, and thymus and activation-regulated chemokine (TARC)/CCL-17. Regression models determined the biomarkers, associated with airflow obstruction (forced expiratory flow at 1 s (FEV\textsubscript{1}%) and FEV\textsubscript{1}/forced vital capacity (FEV\textsubscript{1}/FVC), chronic bronchitis, COPD exacerbations, and emphysema. The authors proved that eotaxin and IL-6 were strongly associated with airflow obstruction; IL-6 was also responsible for the progression of airflow obstruction over 5 years. Both IL-6 and IL-8 were associated with progressive emphysema over 5 years. None of the biomarkers correlated with COPD exacerbations (Table 1).\textsuperscript{35}
Table 1. Biomarkers in COPD patients

| Blood biomarkers                                                                 | Sputum markers                                                                 |
|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Markers associated with disease progression and exacerbation risk**           | **Markers associated with disease progression**                                |
| IL-6, IL-8, IL-16, sRAGE, adiponectin, CC16, EGFR, NET - complex, fibrinogen,   | Higher levels of neutrophil elastase (NE), human neutrophil peptides (HNP),    |
| cotaxin, SP-D, haptoglobin, ceruloplasmin, fibronectin, vitamin D, etc.          | interleukin, IL-8 TNF-α, IL-1 α, IL-1 β, IL-1RA, IL-6, IL17A                   |
| **Markers associated with mortality**                                           | **Markers associated with exacerbation risk**                                |
| White cell count, fibrinogen, CRP, IL-6, IL-8, TNF-α, low eosinophil count <2%  | CXCL9, CXCL10, CXCL11, high neutrophil and macrophage counts, higher levels   |
| hypoalbuminemia, and hypovitaminosis D                                          | of chemotactic protein-1 (MCP-1) and growth-related-oncogene-alpha (GRO-α),   |
|                                                                                 | granulocyte-macrophage colony stimulating factor (GM-CSF), transforming growth |
|                                                                                 | factor (TGF)-β                                                               |
| **Markers responsible for in-hospital mortality in AECOPD exacerbation**        |                                                                                |
| Procalcitonin, high neutrophil to leucocyte ratio, galectin-3                  |                                                                                |
| **Markers associated with tissue turnover**                                     |                                                                                |
| Collagen I and VI fragments, fibrinogen (Aα-Val360)                            |                                                                                |
| **Markers for COPD phenotyping**                                               |                                                                                |
| Low eosinophils - emphysema                                                    |                                                                                |
| Uric acid - never smokers                                                      |                                                                                |
| Eosinophils, IL-33, TLSF, IL-25 - eosinophilic COPD                             |                                                                                |

**Inflammatory markers as predictors of exacerbation risk and mortality**

Three systemic inflammatory markers - CRP, fibrinogen and leukocyte count were tested in the Copenhagen City Heart Study and the Copenhagen General Population Study (n=6574) Their simultaneous elevation increases the risk of frequent exacerbations (OR 3.7).36 These results were validated in milder COPD patients.37 ECLIPSE study established that if added to BODE index, the inflammatory markers (white blood cell counts, fibrinogen, chemokine ligand 18, surfactant protein D, CRP, Clara cell secretory protein-16, IL-6, IL-8, TNF-α), improved its strength to predict mortality.37 Only white cell count, fibrinogen, CRP, IL-6, IL-8, and TNF-α, however, were predictors of frequent exacerbations and higher mortality.38 In a cohort of 493 COPD Danish patients, plasma levels of YKL-40 have been associated with higher all-cause mortality (HR 1.4).39

However, only fibrinogen was validated as a prognostic marker by the US Food and Drug Administration and the European Medicines Agency.40 Kawamatawong et al.41 analysed whether serum inflammatory biomarkers are associated with the clinical outcomes of COPD exacerbation. A total of 62 COPD patients were enrolled. Serum procalcitonin (PCT) and C-reactive protein (CRP) were measured. Dyspnea, eosinopenia, consolidation, acidaemia, and atrial fibrillation (DECAF) score was calculated for predicting mortality. Sputum bacterial culture and polymerase chain reaction for respiratory viruses in nasopharyngeal swabs were performed. In-hospital mortality, invasive mechanical ventilation requirement, and length of hospital stay (LOS) were determined. Serum PCT and CRP, as well as DECAF score were similar in case of viral, bacterial, or co-infection. Neither DECAF score nor serum biomarkers were prognostic for the use of mechanical ventilation, or prediction of mortality. Increased serum PCT was noted in patients with longer LOS ≥7 days.41

Rahimirad et al. studied the significance of neutrophil-to-lymphocyte ratio (NLR), platele-
to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) as predictors of in-hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). NLRs, PLR, LMR, and d-NLR were determined at admission by complete blood count of patients with AECOPD. Multivariate analysis revealed NLR were independently associated with in-hospital mortality. NLR had the highest odds ratio for death both in univariate (OR=3.80) and multivariate (OR=3.50) analyses. PLR and LMR did not show significant relation to in-hospital death in AECOPD. The mortality rate was higher in patients with NLR ≥ 4 than in patients with NLR < 4. Similar data are reported in the study of Yao et al. They determined NLR, PLR, and serum levels of C-reactive protein in a retrospective study of 303 patients with AECOPD. NLR and PLR were significantly higher among non-survivors compared to survivors. At a cut-off value of 6.24, the sensitivity and specificity of the NLR in predicting hospital mortality were 81.08% and 69.17%, respectively.

Mendy et al. also analysed data from 431 COPD patients that were followed up for a median period of 36 months. Several blood biomarkers – CRP, neutrophil and eosinophil counts, plasma albumin and plasma vitamin D levels were measured. Participants with high CRP, low eosinophil count <2%, hypoalbuminemia, and hypovitaminosis D had worse baseline FEV1 and higher mortality in comparison with controls. CRP in addition to eosinophil and/or neutrophil count significantly improved the model for prediction of mortality, independent of age, gender, race/ethnicity, body mass index, smoking and comorbidity (asthma, diabetes, hypertension, and history of stroke or myocardial infarction) (Table 1). 43

SPUTUM BIOMARKERS

Inflammatory markers as predictors of lung function
Sputum has been studied as a non-invasive method of sampling biomarkers. The drawbacks here are that sputum is highly variable in a stable disease and exacerbations, contains a large amount of oral cavity cells and nonviable cells. Besides, not all COPD patients produce spontaneous sputum. Due to confounders, however, (such as smoking status of patients, bacterial infection, concomitant treatment, interference with assays), various results have been found (Table 1).

SPUTUM IN STABLE DISEASE
In a stable disease sputum biomarkers correspond to COPD severity. In the ECLIPSE study, neutrophil count increases with GOLD stage and is weakly associated with lung function. Higher levels of neutrophil elastase (NE), human neutrophil peptides (HNP), interleukin (IL)-8 and matrix metalloproteinase (MMP)-9 in spontaneous sputum of COPD patients predict greater decline in lung function (FEV1). In the ECLIPSE study, gene expression analysis found 277 genes that were differentially expressed between moderate, severe and very severe GOLD classes. 198 were the genes that discriminated severities of emphysema. Although these results were validated in 176 patients, further validation for their clinical utility is required (Table 1).

SPUTUM, EXACERBATION RISK
Inflammatory mediators in induced sputum during stability may predict future risk of exacerbations. Koutskokera et al. found that levels of some mediators in sputum - IL-6, IL-8 and myeloperoxidase (MPO) - may be associated with frequency of exacerbations. In a longitudinal study with monthly visits, sputum levels of leukotriene B4 were elevated prior to an exacerbation, and were suggested as possible biomarkers for exacerbation risk. During exacerbations, sputum cell and cytokine profiles are heterogeneous, deterring the validation of a certain profile (Table 1).

MARKERS FOR COPD PHENOTYPING

Clinical and immunological markers for eosinophilic COPD
A subset of patients with COPD develop eosinophilic inflammation in the airways and have increased blood eosinophil numbers. It could be labelled as a part of asthma-COPD overlap (ACO). However, a recent study demonstrated that eosinophilic COPD patients have distinct characteristics. They have little evidence of allergies and less exacerbations, but more pronounced eosinophilic inflammation (blood eosinophil >2%), higher FEV1 and BMI, higher sputum eosinophils, interleukin (IL)-5 and haptoglobin levels, as well as CCL20 and CCL24 concentrations in BAL. ‘Eosinophil high’ have pronounced airway remodelling as indicated by increased reticular basement thickness, as well as increased BAL metalloproteinase-7 and -9 and IL-33 concentrations. Perez et al. also proved that asthma-COPD overlap (ACO) included patients with COPD and eosinophilic inflammation (e-COPD).
and smoking asthmatics without fully reversible airflow obstruction (SA). They compared e-COPD and SA, regarding their clinical characteristics and inflammatory markers. e-COPD patients were older, predominantly males, with significantly impaired pulmonary function. SA had more atopic features, more reversibility of airflow obstruction and higher IgE levels in comparison to e-COPD. IL-5, IL-13, IL-8, IL-6, TNF-α, IL-17 serum levels were similar in the two groups. However, Th2-engaged biomarkers (periostin, FeNO and blood eosinophils) were higher in the e-COPD patients.50 Similarly, Gao et al. tried to differentiate ACO from COPD and asthma patients analyzing sputum. The percentage of sputum eosinophils was lower in COPD compared to asthma and ACO patients. There was a difference in sputum neutrophil and macrophages percentage among the three groups. No difference in sputum eosinophil counts between patients with ACO and asthma was detected (Table 1).51

Clinical and immunological markers of COPD

Never-smoker phenotype

Lee et al. studied biomarkers representing never-smokers with COPD. A cross-sectional patient cohort study of 131 never-smokers was performed; 77 had COPD. White blood cell count, total bilirubin, interleukin (IL)-6, IL-8, and C-reactive protein, or radiologic measurements (including emphysema index and mean wall area percentage) did not discern never-smokers with COPD from those without. However, the number of subjects with high uric acid was significantly higher in never-smokers with COPD than in those without COPD. High uric acid was significantly associated with the presence of COPD in never-smokers after multivariate analysis (Table 1).52

Markers of COPD emphysema phenotype

Papaioannou et al. evaluated the associations of eosinophils with the presence of emphysema in COPD patients.53 Sputum and blood eosinophil counts, lung function testing and high resolution computed tomography (HRCT) of the chest were performed. Patients with emphysematous lesions engaging ≥15% of the pulmonary parenchyma were assumed as significant emphysema. Ninety-eight patients participated in the study. Patients with significant emphysema had lower blood eosinophil counts compared to patients without emphysema. No difference was observed regarding sputum eosinophils. These data was independent of the frequency of exacerbations or the application of inhaled corticosteroids (Table 1).53

Gene-environmental biomarkers

COPD is driven by an abnormal inflammatory response to noxious particles, implicating that not only smoking but also exposure to air pollution and infectious agents are important triggers for COPD progression and phenotypes. This has led to the exploration of gene – environmental markers, as well as investigation of lung microbiome. Ageing as a result of internal and external factors emerges as a marker of lung/environmental reaction.

Exhaled breath analysis

Volatile organic compounds (VOCs). Exhaled breath analysis, discriminate a range of pulmonary diseases. VOC profiles discriminate COPD phenotypes with either higher sputum eosinophilia or neutrophilia.54 It differentiates COPD subjects with α1-antitrypsin (AAT) deficiency from those that have restored their levels by receiving AAT therapy.55 Sputum cell count and exhaled breath compounds correlate to each other in subjects with mild to moderate COPD (GOLD stages I and II).56 Methodological issues of VOCs testing should be overcome before application in clinical practice.

Exhaled breath condensate (EBC). Collection of cooled exhaled breath condensate is a noninvasive approach of sampling the airway lining fluid. EBC acidification could be a marker of airway inflammation and disease severity in COPD. EBC hydrogen peroxide (H2O2), a marker of oxidative stress, correlates with the COPD health status, determined by COPD assessment test (CAT). It is also reduced during acute exacerbations.57

Gao et al. studied 163 patients with COPD exacerbation. All patients underwent the following: FeNO test, spirometry, bronchodilator reversibility test, induced sputum, and routine blood tests. They were classified as eosinophilic group or non-eosinophilic group based on sputum eosinophilic percentage (≥2.5%). Gao et al. established that inflammatory biomarkers, including sputum eosinophilic percentage, FeNO level, and blood eosinophilic percentage, can be used to positively diagnose eosinophilic COPD. The authors describe that sputum eosinophilic percentage was higher in patients with high FeNO (FeNO >32 ppb) in comparison to those with FeNO <32 ppb. Eosinophils in induced sputum correlated with both FeNO levels and blood eosinophilic percentage. Blood eosinophilic percentage and FeNO
levels were predictive of sputum eosinophilia. Validation of assays, however, as well as interpretation of clinical impact require solution before implementation in practice.

**EXPOSURE TO AIR POLLUTION**

In up to 25-45% of patients with chronic airflow limitation, non-smoking-related factors (e.g., air pollution) play the leading role in disease progression. In the urban environment vehicle emissions contribute to air pollution. Particulate matter less than 10 μm in diameter, nitrogen dioxide (NO₂) and sulfur dioxide (SO₂) are assumed as major contributors. In addition to cigarette smoking, their repetitive inhalation may be assumed as a trigger for progression. Long-term exposure to particulate matter reduces lung function and increases COPD incidence. Exposure to air pollution in susceptible individuals is a trigger for COPD progression. EBC levels of nitrite and nitrate (markers of oxidative stress) were associated with concentrations of ambient coarse particles. Blood levels of CRP, fibrinogen, HGF and IL-8 correlated to increased ambient NO₂ levels, mainly in stable COPD former smokers.

**LUNG MICROBIOME**

Bacteria can be isolated in 50% of cases with acute COPD exacerbations. Colonisation of the airways is often encountered in severe COPD patients. It is assumed that chronic microbial colonisation alters innate immunity. It makes the airway epithelial more vulnerable and contributes to disease progression. Thus, even in stable disease bacterial infection promotes inflammation. Microbiome includes all the microbes that share common environmental conditions in a particular body site. Microbes, including unculturable, can be detected by nuclear acid sequencing. Various regions of the 16S gene, which encodes bacterial ribosomal RNA (rRNA), is mostly applied. Explorations of microbiome in COPD and non-COPD subjects showed that tobacco smoking in the absence of COPD does not alter lung microbiome. RSV infections increase bacterial load in COPD, but preserve bacterial diversity. The predominance of bacterial species in a separate anatomical region of the lung, may reduce bacterial diversity and cause dysbiosis – imbalance between mucosal immunity and bacterial communities. In severe COPD, resident bacterial communities are less diverse. Changes in the normal balance of bacterial flora may lead to an excessive inflammatory response perpetuating inflammation in COPD.

Similar data were presented by Wang et al. Sirtuins and telomere shortening are mostly studied, as they relate to lung ageing in COPD patients. Telomerases are composed of repetitive sequences and are protective structures that stabilise chromosome ends. During cell division telomere repeats physiologically shorten. Peripheral blood leukocytes of COPD patients have shorter telomeres. In comparison to controls, COPD patients had shorter telomeres and their length more strongly correlated with lung function in never smokers than in smokers. In the Lung Health Study (n=4271) short leukocyte telomere length was associated with increased risk of all-cause mortality (HR 1.29), compared to longer telomeres in 4271 subjects with mild-to-moderate COPD. A study of 46396 subjects found an association between reduced leukocyte telomere length and COPD. A weak association between telomere length and lung function (FEV₁; FEV₁/FVC) was described.

Sirtuins (SIRTs) are histon-deacetylases with seven homologues in man - SIRT1-7. These enzymes belong to silent information regulator family – Sir2 and are responsible for gene silencing. SIRT1 is thoroughly explored in humans and possesses anti-inflammatory and anti-ageing effects. In COPD lung tissue and peripheral blood mononuclear cells, its levels are decreased. Sirtuins provide resistance to oxidative stress and DNA repair. They regulate matrix metalloproteinases expression. MMP-9 is down-regulated by SIRT1, therefore reduced levels of SIRT1 may cause extracellular damage in lung tissue. In the large airways of asymptomatic smokers sirtuin expression is decreased. This, however, cannot be observed in the small airways. In contrast, in COPD, sirtuin levels are even lower, in both large and small airways. Thus, sirtuin expression is involved in accelerated lung ageing and COPD pathogenesis. In addition to the low levels of sirtuin in COPD lungs, Yanagisawa et al. have also proved that in COPD patients serum sirtuin levels are also significantly diminished. They investigated serum sirtuin levels in 12 never smokers, 19 smokers without COPD and 26 COPD patients. Western blot analysis was performed. Authors describe that serum sirtuin levels in COPD patients are lower than in healthy smokers or non-smokers. Sirtuin serum levels correlated positively with FEV₁, BMI, diffusion capacity. They are lower in COPD patients with emphysema and frequent exacerbations.
PERSPECTIVES

THE NEW VERSION OF AN OLD STORY – COPD AS AN AUTOIMMUNE DISEASE

There is growing evidence that autoimmunity has a role in the pathogenesis of stable COPD, but no cause-and-effect relationship between autoimmunity and COPD mechanisms has been established. It is assumed that oxidative, nitrosative stress and endogenous sources may cause direct tissue damage. A post-translational, non-enzymatic modifications on proteins ensues. Neo-autoantigens are formed that trigger an autoimmune response in the lower airways of smokers. With the progression of the autoimmune response, there is deposition of immune complexes within the lower airways and the local activation of cell-mediated autoimmune damage causes lower airway chronic inflammation. In susceptible subjects this is associated with a slowly progressive remodelling of the lower airways (chronic bronchiolitis and pulmonary emphysema) and by the clinical diagnosis of COPD. B-cells are found to be localized in the peripheral lung of stable COPD. A predominant part of these cells are memory B-cell. B-cells accumulate in the lungs and contribute to cigarette smoke (CS)-induced pulmonary emphysema. B-cell deficient mice are protected against CS-induced emphysema. There are increased numbers of activated signal transducer and activator of transcription-4 and IFN-g CD4+ T cells in COPD patients. Thus, activated T-cells, along with CD8+ T cells and innate immune cells recruited by Th1 cytokines, damage the lung. Severe emphysema has been associated with lung oligoclonal CD4+ and CD8+T cells.

MICROPARTICLES – FLOATING MESSENGERS IN COPD PATHOGENESIS

Extracellular vesicles (EVs) play a role in the pathogenesis of lung diseases. They are plasmic membrane fragments released from cells after physiological or stress conditions. Their production correlates to the rate of cell apoptosis. All types of cells produce MP, but platelets, endothelial cells, and leukocytes are major producers. They include exosomes, ectosomes (ie, microparticles, extracellular vesicles, microvesicles, and shedding vesicles), and apoptotic bodies. Exosomes are generated by inward budding of the membrane (endocytosis), and release by exocytosis. Ectosomes are formed by outward blebbing from the membrane and proteolytic cleavage from the cell surface. Apoptotic bodies are generated on apoptotic cell death. Extracellular vesicles are released when the cells are activated or undergo apoptosis under inflammatory conditions. The number and types of released EVs are different according to the pathophysiological status of the disease. EVs contain several molecules (mRNA, microRNA, and DNA) that are transferred to distant recipient cells. They modify the targeted cells and influence the microenvironment of the lungs.

Tan et al. evaluated the level of circulating exosomes in relation to systemic inflammation in patients with AECOPD, or stable COPD in comparison to non-smoking healthy controls. C-reactive protein, tumour necrosis factor receptor-1 (sTNFR1) and interleukin (IL)-6 were also quantified. Levels of plasma exosome were higher in AECOPD patients and sCOPD patients compared to controls. Plasma levels of CRP and sTNFR1 were the highest in AECOPD, followed by sCOPD patients compared to healthy controls. The level of exosome correlated with the levels of CRP, sTNFR1 and IL-6 in plasma.

CONCLUSION

Thanks to the development of new technologies, biomarker research in COPD is not illusive. Though inspiring, results should be analysed cautiously, as they may seem confusing at first glance. The reason for this is that studies are performed in different disease states, among patients with different COPD activity and severity. This, alongside, with the lack of validated kits for sputum and BAL, as well as with the technical limitations of the contemporary biotechniques, makes biomarker sphere useless until now. To become real and applicable into clinical practice data should be generated from studies with well characterized phenotypes of COPD patients, with relatively similar disease severity and health status impact, using validated kits and well established biotechnologies. According to the US Food and Drug Administration and the European Medicines Agency, only fibrinogen is currently being validated as a prognostic marker in COPD. Thus, the standardization of biomarkers for COPD and their practical utilization into clinics remains a challenge.

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Биомаркеры при ХОБЛ - противоречивые, реальные или иллюзорные

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Изучение биомаркеров для ХОБЛ стало самой быстроразвивающейся областью медицины болезней лёгких. Хотя «омики» генерируют огромное количество биомаркеров, фибриноген является единственным, утверждённым Европейским агентством по лекарственным средствам. Тысячи исследований, анализирующих различные биологические образцы дыхательных путей, взятые с использованием различных методов, инструментов и техник, генерируют все больше и больше данных, что делает биомаркеры очень противоречивыми, а не практическими. По-видимому, для того, чтобы стать применимым и утверждённым, биомаркеры должны быть анализированы в точно описанной группе пациентов, однородных по тяжести и активности болезни. Поскольку ХОБЛ имеет многочисленные механизмы патобиологии, возникает вопрос о том, какой из них является наиболее подходящим биологическим образцом, который отражает каждый из них. Должны быть введены единые критерии взятия проб тканей, проверенные инструменты для зондов дыхательных путей и стандартизированные технологии. Данное обозрение представляет биомаркеры, которые в настоящее время являются утверждёнными и ставит проблему стандартизации.