Lymphocyte subpopulations in community-acquired pneumonia: role of cell-mediated immunity

SUMMARY

Lymphopenia has been recently recognized as an immunological community-acquired pneumonia (CAP) phenotype associated with mortality although there is a lack of information on specific lymphocyte subpopulations involved. We aimed to characterize the lymphocyte subpopulations at CAP diagnosis and its relationship with host inflammatory response.

Prospective study conducted in a Spanish hospital including immunocompetent patients hospitalized for CAP. We collected data on demographics, comorbidities, initial severity and 30-days mortality. Lymphocyte subpopulations (CD4, CD8, CD19 and NK cells) and cytokines (TNF-α, IL-1β, IL-2, IL-4, IL-5, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, IFN-γ and MCP-1) were analyzed within the first 24 h after admission.

217 patients were recruited of whom 128 (59%) had sepsis and 12 (5.5%) died during the first 30-days. 128 patients had lymphopenia (<1000 lymphocytes/μL). A significant reduction in CD4, CD8 and NK cells was found in patients with sepsis. Patients with lymphopenia showed higher concentrations of IL-2, IL-8, IL-10, IL-17, G-CSF, MCP-1 and MIP-1β in comparison to those without lymphopenia. An inverse correlation was found between absolute lymphocyte count and IL-8 (rho: -0.285; p<0.001), IL-10 (rho: -0.245; p<0.01, G-CSF (rho: -0.246; p<0.01) and MCP-1 (rho: -0.242; p<0.001). 57.1% of survivors vs 91.7% of non-survivors presented lymphopenia (p<0.05). Non-survivors showed significant lower counts of CD4, CD8 and NK cells than survivors.

A reduction in T and NK cells cause lymphogenic-CAP with a concomitant higher inflammatory response and worse prognosis. In the future, immunotherapy for T and NK cells restitution in CAP should be explored to improved survival.
Mortality in CPAP-treated patients at the population level: Analysis of all CPAP-treated patients in Catalonia

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SUMMARY
Obstructive sleep apnea (OSA) has been associated with increased rates of morbidity and mortality due to its association with hypertension, cancer, and metabolic, cardiovascular and cerebrovascular diseases. The application of nocturnal continuous positive airway pressure (CPAP) effectively improves daytime symptoms and quality of life of OSA patients and moderately decreases arterial blood pressure in OSA patients with resistant hypertension. However, whether CPAP treatment reduces mortality at the population level remains unclear.

A total of 70,469 CPAP-treated patients and 184,112 controls matched (1:3) on 5-year age-group, gender and health region, attended by CatSalut during 2012-2013 were assessed to determine the relationship between CPAP treatment and mortality. Data on 2012-2013 comorbidities, and 2012-2015 mortality were recorded. CPAP treatment was associated with reduced mortality in a multivariable logistic regression model adjusted for age, sex and relevant comorbidities (OR=0.867; 95% CI: 0.813-0.924). Significant interactions between CPAP treatment and cerebrovascular diseases (OR=0.621; 95% CI: 0.546-0.707), diabetes mellitus (OR=0.742; 95% CI: 0.675-0.815) and hypertension (OR=0.776; 95% CI: 0.725-0.830) were found. However, CPAP-treated patients showed lower mortality rates than controls in all scenarios, with greater differences at advanced ages.

The population of CPAP-treated patients in Catalonia had lower mortality rates than age-, gender- and region-matched controls, despite a higher prevalence of most comorbidities among CPAP-treated patients, thus suggesting that CPAP treatment successfully reduces mortality at the population level. However, further analyses should be planned to clarify which OSA patients could benefit the most from CPAP treatment and whether CPAP might be detrimental in some specific patient subgroups.
Imbalance between purinergic signalling enzymes as a main inflammatory trigger in COP

INTRODUCTION

Growing evidence indicates the involvement of extracellular ATP and adenosine in the pathogenesis of obstructive airway diseases, but its role in COPD is unknown. Extracellular ATP, which acts as a pro-inflammatory molecule through P2 receptors, is sequentially hydrolyzed into adenosine by ectonucleotidases (such as E-NTDPases, E-NPP1 and CD73). Adenosine has anti-inflammatory effects through P1 receptors and is hydrolyzed into inosine by ADA enzyme. We hypothesized that the expression of genes controlling extracellular ATP and adenosine levels are altered in COPD.

METHODS

Quantitative real-time PCR was performed to analyze the relative expression of purinergic signaling and inflammatory related genes in lung tissue samples of COPD patients (n=14), non-obstructed smokers (NOS) (n=13) and never smokers (NS) (n=8).

RESULTS

In COPD, gene expression of ATP degrading enzymes ENTPD-1 and -2 were decreased compared to other groups. CD73 expression was increased in NOS compared to COPD and NS. All P2 receptors analyzed were less expressed in COPD. The expression of ADA enzyme was decreased in COPD and NOS. Differences in P1 receptors expression were found: ADORA1 expression was decreased in COPD, while ADORA3 was increased in COPD and NOS. No differences in the expression of ENTPD3, ADORA2A and ADORA2B were found between groups. Inflammatory genes expression, as Interleukin-13, were up-regulated in COPD compared to other groups.

CONCLUSIONS

The expression pattern of different extracellular ATP degrading enzymes are altered in smoker groups (NOS and COPD) promoting inflammation. The high CD73 expression found only in NOS could compensate an inflammatory environment.
Comparative study of metabolomics of lung cancer: based on serum, urine and bronchoalveolar lavage fluid

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**PURPOSE**

Lung cancer (LC) is one of the most common causes of death by neoplasia. The use of metabolomics provides overall information about the metabolic disorders caused by the LC. We applied a metabolomic approach based on gas chromatography coupled to a mass spectrometry (GC-MS) to determine the metabolomic profile in three biological fluids from patients with LC: serum (S), urine (U) and bronchoalveolar lavage fluid (BALF).

**DESCRIPTION**

Treatment of fluids samples was based on the addition of alcoholic solvents to separate the protein fraction after centrifugation, and urease in the case of the urine. Finally, derivatization by methoximation for the protection of carbonyl groups and silylation of polar groups to convert them to volatile compounds was performed before the injection into GC-MS.

90 serum, 90 urine and 55 BALF samples from patients with LC, patients with lung diseases NO cancer (LD), and healthy controls (C), were analyzed in order to compare the metabolomic profiles of these three types of samples. Multivariate analysis, PLS-DA, showed a clear classification of study groups, indicating the existence of altered metabolites in LC. We identified 22, 18 and 20 perturbed metabolites in LC group were identified in S, U and BALF, respectively, involving different metabolic pathways associated with LC.

**RESULTS**

Metabolic pathways indicated that the metabolism of glycine, threonine and serine was the most disturbed in LC. In addition, evaluation of specificity and sensitivity of altered metabolites by ROC (receiver operator characteristic) curves were applied to characterize potential biomarker of LC.

**CONCLUSIONS**
A systems approach to non-pulmonary manifestations of COPD: biological mechanisms, health risk assessment, and clinical management

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The Synergy-COPD project was conceived as a systems medicine approach to study non-pulmonary phenomena observed in patients suffering from chronic obstructive pulmonary disease (COPD). The overarching hypothesis was that non-pulmonary manifestations cannot solely be explained by the activity of the pulmonary disease. The project addressed underlying biological mechanisms of skeletal muscle dysfunction and the phenomenon of co-morbidity clustering. It was designed as an iterative analysis of data from animal experimentation, human studies, epidemiological research and registry datasets. This abstract summarizes the biomedical outcomes of the project.

Synergy-COPD identified abnormalities in co-regulation of core biological pathways (i.e., bioenergetics, inflammation and tissue remodeling) operating as central players in non-pulmonary manifestations. In particular, several lines of evidence support a relevant role for oxidative stress as a key characteristic mechanism in these patients. The findings showed significant associations with aerobic capacity, but not with lung function. In addition, a data-driven analysis of the Medicare dataset (13M patients over 65 years) indicated higher risk for co-morbidities in patients with COPD, and a population-health risk assessment of COPD cases (n= 264,830) in Catalonia (ES) (7.5M citizens) suggested a high predictive role of co-morbidities in terms of mortality, hospitalizations (related and not related to COPD), multiple hospital admissions, and high healthcare costs.

These findings on mechanisms of non-pulmonary phenomena and co-morbidities, pave the way of novel risk assessment strategies. Synergy-COPD strongly points out the need for complementing current lung-based standards of clinical management with a broader vision based on a patient-oriented approach focused on comorbidity prevention.
Prevalence of obstructive sleep apnea (OSA) in patients with lung cancer. Results from the prospective sail study (sleep apnea in lung cancer)

Authors


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INTRODUCTION

OSA has been linked to oncogenesis and tumor proliferation. The SAIL study (NCT02764866) investigated the prevalence of OSA in patients with lung cancer.

PATIENTS & METHODS

The SAIL study was designed as a prospective observational study to determine the prevalence of OSA in patients with lung cancer prior to initiating oncologic treatment. All patients were offered home sleep apnea testing (HSAT) with the NOx T3 device and completed a sleep specific questionnaire. Pertinent epidemiologic, respiratory, oncologic and sleep variables were recorded.

RESULTS

Eighty-three patients signed informed consent and 60 patients completed HSAT. Most were male (58%) with a mean age of 68 years and mean BMI of 28.1 kg/m². Mean tobacco exposure was 54 pack-years. 50% had COPD with a mean FEV1 of 83% of predicted and a diffusing capacity of 85.5%. Adenocarcinoma (46.7%) was the most common histology type, followed by squamous cell (16.7%), and small cell LC (16.7%). 43.3% were stage IV and only 32% were stage I-II. Eighty percent of patients had OSA (AHI>5) and 50% had moderate to severe OSA (AHI>15) with mean Epworth scores of 7.43. AHI was inversely correlated with tumor stage and desaturation indices (p=0.01).

CONCLUSIONS

OSA is very prevalent in lung cancer and its severity appears inversely correlated with tumor stage.
MicroRNA profile of cardiovascular risk in patients with obstructive sleep apnoea

INTRODUCTION

Obstructive sleep apnoea (OSA) is a disease caused by repeated episodes of collapse of the upper airway during sleep and is associated with development of cardiovascular events (CVE). There is a high heterogeneity in the impact of OSA in cardiovascular disease (CVD). Until now, the profile of the OSA patient has not been defined at risk of developing a CVD and what are the variables that could be used to predict the CV risk of a patient with OSA.

Aims: To identify the microRNA (miRNA) profile associated with CVD in patients with OSA.

Methodology: Observational, cross-sectional study that includes patients who represent the natural history of OSA and CVD. Four groups of patients were defined: Healthy, non-hypertensive OSA, OSA with hypertension and hypertensive OSA with CVE. RT-qPCR TaqMan Low Density Arrays (Applied Biosystems) of 188 miRNAs was also performed. Groups were homogeneous for sex, age and body mass index.

Results: An initial miRNA profile of 10 patients per group was performed. From the 188 miRNAs analyzed, a specific signature of miRNAs was established for each group. Moreover, this preliminary analysis showed the existence of a set of 4 miRNAs that provide a discriminatory model of cardiovascular risk profile.

Conclusions: Our preliminary results suggest the existence of a specific miRNA signature that could identify the CV risk profile of a patient with OSA. This signature could provide a useful tool for the identification of the OSA patient at CV risk. These preliminary results should be further confirmed.

Supported by: This work was supported by Fondo de Investigación Sanitaria (Fondo Europeo de Desarrollo Regional (FEDER) [PI14/01266]), the Spanish Respiratory Society (SEPAR) [061/2014], the Catalanian Respiratory Society, Desarrollo Tecnológico en Salud [DTS15/00145], IRB Lleida Biobank and Associació Lleidatana de Respiratori (ALLER).
Systemic biomarkers in bronchiectasis exacerbations: a comparison between hospitalized and outpatients

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RATIONALE
Bronchiectasis (BE) is a chronic structural lung disease that course with exacerbations provoking an increase in local and systemic inflammation. We aimed to investigate the systemic inflammation in BE exacerbations in hospitalized and outpatients.

METHODS
Prospective study conducted in adult patients with bronchiectasis attended in two tertiary care university hospitals. We included BE exacerbations treated at the hospital and in the outpatient clinic. We collected data on demographics, comorbidities, bronchiectasis severity scores and microbiological etiologies. Inflammatory biomarkers (proadrenomedullin, procalcitonin, CRP, TNF-α and interleukin-8) were analyzed: during the exacerbation at day 1 and day 5, and at 30 and 60 days during the follow-up.

RESULTS
We included 165 patients: 72 outpatients and 93 admitted to hospital. We analyzed the kinetics of cytokines and inflammatory markers. (Table 1)

CONCLUSIONS
PCR showed high initial levels during exacerbations, regardless hospitalization, with a posterior decrease at 30 and 60 days.

In hospitalized exacerbation; proADM systemic levels were increased during exacerbation and at days 30 and 60 while IL-8 and TNFα levels were raised during the follow-up and PCT only within exacerbation and at 30 days.

Systemic biomarkers in BE exacerbations showed some differences depending on hospitalization requirement with a relative sustained increase during 60 days.
<table>
<thead>
<tr>
<th></th>
<th>OUTPATIENTS</th>
<th>INPATIENTS</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>DAY 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>TNF-α</td>
<td>6.70(4.80-8.77)</td>
<td>6.15(4.24-11.19)</td>
<td>0.800</td>
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<tr>
<td>IL-8</td>
<td>7.16(4.75-10.26)</td>
<td>7.49(5.20-11.45)</td>
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<tr>
<td>Proadrenomedullin (nmol/l)</td>
<td>0.75(0.59-0.98)</td>
<td>1.11(0.84-1.38)</td>
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</tr>
<tr>
<td>Procalcitonin (microg/L)</td>
<td>0.13(0.11-0.18)</td>
<td>0.19(0.14-0.51)</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP(mg/L)</td>
<td>45.84(17.66-98.73)</td>
<td>66.08(19.54-144.29)</td>
<td>0.123</td>
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<tr>
<td><strong>DAY 5</strong></td>
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</tr>
<tr>
<td>TNF-α</td>
<td>6.04(4.43-7.83)</td>
<td>5.96(4.36-8.66)</td>
<td>0.783</td>
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<tr>
<td>IL-8</td>
<td>5.06(3.71-7.83)</td>
<td>5.79(4.20-9.65)</td>
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<tr>
<td>Proadrenomedullin (nmol/l)</td>
<td>0.66(0.50-0.89)</td>
<td>0.97(0.78-1.33)</td>
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<tr>
<td>Procalcitonin (microg/L)</td>
<td>0.12(0.10-0.16)</td>
<td>0.15(0.12-0.25)</td>
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<tr>
<td>CRP (mg/L)</td>
<td>9.27(4.45-26.85)</td>
<td>12.00(4.85-33.69)</td>
<td>0.291</td>
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<td><strong>DAY 30</strong></td>
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<tr>
<td>TNF-α</td>
<td>5.62(4.26-8.35)</td>
<td>7.20(5.21-10.78)</td>
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<tr>
<td>IL-8</td>
<td>5.45(3.48-7.81)</td>
<td>8.17(5.33-18.03)</td>
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<td>Proadrenomedullin (nmol/l)</td>
<td>0.64(0.57-0.82)</td>
<td>0.90(0.77-1.21)</td>
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<tr>
<td>Procalcitonin (microg/L)</td>
<td>0.11(0.09-0.14)</td>
<td>0.13(0.11-0.16)</td>
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<tr>
<td>CRP (mg/L)</td>
<td>2.26(1.22-7.15)</td>
<td>8.55(1.96-23.29)</td>
<td>0.004</td>
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<td><strong>DAY 60</strong></td>
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<tr>
<td>TNF-α</td>
<td>5.73(3.80-7.47)</td>
<td>7.43(6.31-9.79)</td>
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<td>IL-8</td>
<td>5.37(4.07-6.77)</td>
<td>6.84(5.80-10.19)</td>
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<td>Proadrenomedullin (nmol/l)</td>
<td>0.64(0.54-0.80)</td>
<td>1.05(0.82-1.16)</td>
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<tr>
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<td>CRP (mg/L)</td>
<td>2.99(1.63-7.70)</td>
<td>6.49(3.37-14.01)</td>
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Prevalence and impact of COPD in patients with acute myocardial infarction

Authors
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OBJECTIVE
To estimate the prevalence and level of underdiagnosis of COPD in patients with acute myocardial infarction (AMI), and to analyze the phenotypic and multidimensional characterization, mortality and level of undertreatment.

MATERIAL AND METHODS
Non-post-authorization (non-EPA), prospective, multicenter, multidisciplinary study of patients diagnosed synchronously with COPD and AMI. Descriptive analysis of the variables studied, parametric/nonparametric tests, and Kaplan-Meier tables for survival. Analysis by SPSS 22.0 and Epidat 4.1 (significant p <0.005).

RESULTS
Of 467 patients with AMI, 95 (20.34%) were COPD. Of these, mean age 74.28 years (± 11.02), men 82 (86.32%), smoking 71.58%, packages/year 50.92 (± 28.79); in non-smokers 7 exposure to biomass combustion smoke. Previous diagnosis of COPD (24.21%). Phenotypes GESEPOC: No exacerbator: 78 (82.11%), Mixed 4 (4.21%), Exacerbator type emphysema 6 (6.32%) and type chronic bronchitis 7 (7.37%). Severity: Mild 58 (61.05%), Moderate 26 (27.37%) and Severe 11 (11.58%). The patients were significantly older (p <0.001), smoking (p <0.028), dyspnea (p <0.001), Charlson index (p <0.001) and heart failure (p <0.009); lower use of antiplatelet agents (p <0.001) and higher anticoagulants (p <0.002) and bronchodilators (p <0.001), without differences in the rest of the treatments performed. Tendency to lower survival without reaching statistical significance (p = 0.051).

CONCLUSIONS
1. Prevalence of COPD of 20.34%.
2. Important underdiagnosis, and probable overdiagnosis with current spirometry criteria.
3. Most are mild non-exacerbating COPD. There is no undertreatment.
Bronchial hyperreactivity in COPD: Impact on survival

Authors

OBJECTIVE
To analyze the frequency of bronchial hyperresponsiveness in COPD patients and to evaluate its influence on the long-term prognosis.

METHODS
Of the patients with COPD who attended a functional respiratory exploration between 01/01/2011 and 06/30/2011, those with a FEV1 < 70% who had bronchial hyperresponsiveness criteria (increased FEV1 more than 12% and more than 200 ml after the bronchodilator test) were collected. Its frequency and its influence on survival were analyzed using the Kaplan-Meier method and the Cox regression, in order to identify risk factors for mortality.

RESULTS
We studied 273 patients (11% women) with a mean age of 67.9 ± 10.6 years. The mean FEV1 was 48.6 ± 12.6%. Twenty-seven percent had bronchial hyperresponsiveness. In this group, the 6-year survival was 81.5%, being only 64.7% in the group of patients without bronchial hyperresponsiveness (p < 0.05). Patients with bronchial hyperresponsiveness had a HR = 0.53 (95% CI = 0.28 - 0.99) regardless of age, sex and lung function.

CONCLUSIONS
The presence of bronchial hyperresponsiveness in COPD patients with FEV1 < 70% has a favorable impact on the prognosis of these patients, and it is associated with a greater long-term survival.
Cancer-related genomic alterations (driver-mutations), frequently found in lung adenocarcinoma (ADK), are molecular alterations that affect oncogenes and produce a clonal expansion in the cells affected. Our group was the first to demonstrate the presence of these mutations in non-tumoral lung cells (last year abstract).

**OBJECTIVE**

To identify whether the presence of driver-mutations in non-tumoral cells of patients with lung ADK are related with worst disease-free-survival (DFS) and time-to-progression (TTP) after one year of resection in stage-I cancer patients.

**MATERIALS**

Between 2009-2015 expanded molecular profile (*EGFR-KRAS-BRAF-ROS1-ALK-MET-RET*) was performed to 625 patients with adenocarcinoma. 47 had *KRAS-EGFR* mutations and underwent resection. After carried out highly-specific/sensitive CastPCR in normal parenchyma, we followed-up our cohort with CT-scan at 3-6-12 months for recurrence and pertinent tests when suspicion of metastasis.

**RESULTS**

In 10 patients (21.3%) the same driver mutations were identified in tumor and normal parenchyma (SDM). These patients presented a much higher recurrence rate (distant metastases occurred in 60 vs. 5.4% in SM and non-SM groups, p<0.001). Kaplan-Meier analysis showed that TTP was lower (8.5 vs. 11.7 months, p<0.001) and the DFS was also significantly poorer (8.5 vs. 11.2 months, p<0.001) in the SM group. COX regression showed a higher progression or death risk (HR: 5.94, p<0.01) and after adjusting for sex, age, lymph vascular invasion and postoperative stage the patients maintained the risk.

**CONCLUSION**

The cancer-related mutations when occurred in the normal lung tissue of patients with stage I ADK is related with a much worse prognosis than the group without the mutations.
The soluble RAGE as a discriminative serum marker in the diagnostic of interstitial lung diseases

INTRODUCTION

The soluble receptor for advanced glycation end-products (sRAGE) is an immunoglobulin implicated in the maintenance of alveolar structures. The imbalance between this receptor along with its ligand AGE, has been associated with accelerated aging in lung samples from idiopathic pulmonary fibrosis (IPF). We analyzed the potential role of sRAGE-AGE ratio in serum as a biomarker to discriminate between different interstitial lung diseases, such as IPF, fibrotic nonspecific interstitial pneumonia (fNSIP) and chronic hypersensitivity pneumonitis (cHP).

METHOD

Serum samples were collected from adult patients: 48 IPF, 15 cHP, 15 fNSIP, and 12 healthy controls. Patient characteristics (age, sex, smoke habits, and respiratory functional test) were also recorded. ELISA for AGEs and sRAGE were assessed in all samples and data were correlated with demographic and respiratory parameters.

RESULTS

Our study demonstrated a decrease in sRAGE serum concentration together with an increment of AGEs concentration in IPF and cHP compared with control and fNSIP patients. In this way, the AGE-sRAGE ratio was greater in IPF and cHP group in comparison with control and fNSIP. The correlation between AGEs and sRAGE serum concentration was negative in IPF samples. Moreover, less sRAGE serum concentration correlated with a poorer respiratory function test (FVC and DLCO) in the analyzed interstitial lung diseases, statistically significant in IPF.

CONCLUSION

These findings demonstrate that the serum imbalance in sRAGE-AGE ratio could differentiate between IPF and fNSIP. Furthermore, the concentration of sRAGE in blood stream could reflect the progression of the interstitial lung disease.
Frequency and risk factors associated to Interstitial Lung Abnormalities (ILA) in asymptomatic older (>60 years) individuals

Authors
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RATIONALE
Interstitial lungs abnormalities (ILA) have been identified by chest computed tomography (CT) scans in around 7% of older asymptomatic individuals. However, its bio pathological consequence and long-term outcome is yet unclear.

AIM
To determine the prevalence of ILA in a cohort of asymptomatic Mexican subjects above 60 and identify genetic and environmental risk factors likely associated.

METHODS
From a prospective, ongoing, lung-aging study of asymptomatic subjects, we reviewed CT scans of 583 participants to identify patterns of ILA. This abnormality was defined as the presence of nondependent ground glass opacities (non-fibrotic ILA) and/or reticular abnormalities (fibrotic ILA) affecting more than 5% of any lung zone. Demographic characteristics, lung function tests, common variants rs35705950 from MUC5B and others, serum levels of some biomarkers were compared with non-ILA subjects of the same cohort. Significant differences were analyzed by non-parametric statistic p<0.05.

RESULTS
45 individuals (8%) were classified as fibrotic ILA, one of them showing combined idiopathic pulmonary fibrosis and emphysema and two other evolving to early IPF/UIP in few months after initial evaluation. There were no significant differences among age, gender, tobacco exposure and GERD. Patients with ILA showed a high frequency of the MUC5B polymorphism (OR 4.48, CI95% 1.21-16.79, p=0.014) and an increase of MMP-7 serum concentrations.

CONCLUSIONS
Our findings corroborate that a group of older asymptomatic individuals present interstitial lung abnormalities on CT scan. Common variants of MUC5B seem to be associated with increased risk. Cigarette smoking did not appear to influence the development of ILA.
Differential bone marrow network response in patients with COPD

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BACKGROUND
Bone marrow (BM) produces hematopoietic stem cells and endothelial progenitor cells (EPCs) both with capacity of self-renewal and differentiation. These cells represent the main source of circulating progenitor cells with tissue repair capacity. Their role in COPD is uncertain.

OBJECTIVES
We aimed to analyze the cellular and functional characteristics of BM in COPD patients. A subgroup analysis of COPD patients based upon the presence of emphysema (DLCO pred <60%) or blood eosinophilia (eosinophil (Eos) count ≥300 cells/microL) was anticipated.

METHODOLOGY
Case-control study with consecutive recruitment of patients undergoing cardiothoracic surgery. Fine-needle BM aspiration was performed. Cell count was determined by microscopy, cell immunophenotype by flow cytometry, systemic inflammation (C-reactive protein, IL-6, IL-8) and repair (HGF, IGF, TGF-β, VEGF) markers by ELISA. These variables were correlated with pulmonary function and inflammatory parameters using a network approach.

RESULTS
Thirty-five COPD patients, 10 smokers and 15 non-smokers controls with normal lung function were studied. We found a positive correlation between HGF measured in BM and HGF in peripheral blood, bone marrow endothelial progenitor cells and lung function (FEV1 and DLCO). Regarding subgroup analysis, COPD patients with eosinophilia presented a reduced proportion of a proliferation marker (CD34+c-kit+) and poorer lung function compared to COPD without eosinophilia.

CONCLUSIONS
This study shows that the bone marrow could participate in the repair process in COPD and that eosinophilia could be a determining factor.
Bronchial colonization and regional variability in the respiratory microbiome of cystic fibrosis

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OBJECTIVE
To compare the microbiome of upper (nose and throat) and lower (sputum) airways in Cystic Fibrosis (CF) patients to identify potential differences in bacterial composition.

METHODS
Cross-sectional study of 15 clinically stable (>8-weeks) CF patients, with FEV1>40% and not treated with systemic corticosteroids. Sputum (S) was cultured and samples from different respiratory tract regions, including nasal lavage (N), oropharyngeal swabs (OF) and S, were analyzed using 16S rRNA gene sequencing.

RESULTS
CF patients had a mean age of 17 (SD 10) years and FEV1% 88 (SD 20). 12 had pancreatic insufficiency (80%). The phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, TM7, Acidobacteria, Chloroflexi y Planctomycetes showed a median RA over 1% in at least one type of sample. Beta-diversity analysis showed significant differences in the microbial composition between bacterial communities in different regions (p=0.001, Adonis test). N diverge markedly from OF (distance θYC: 0.87 [IQR:0.71-0.96]) and S (distance θYC: 0.63 [IQR:0.54-0.77]), while OF and S (distance θYC: 0.63 [IQR:0.54-0.77]) showed a closer similarity. S. aureus culture-positive sputum samples showed low relative abundance (RA) of Staphylococcus, but significantly higher than culture-negative samples (median: 0.68 (IQR:0.43-3.19) vs. 0 (IQR:0.0-0.03), p<0.001 Mann-Whitney test).

CONCLUSION
The bacterial communities of the nose, throat and sputum in CF patients have clear-cut differences, and bronchial colonization by Staphylococcus aureus is not associated with RA over 5% in this genus.
Gene expression profile in peripheral blood of COPD patients with and without eosinophilia

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COPD is a heterogeneous condition with distinct clinical and pathophysiological features. Although the airway inflammatory pattern has been typically associated with neutrophilic predominance, eosinophilic inflammation has also been recognized as a COPD endotype (30-40% of patients). This endotype can be detected by an increase in the number of blood eosinophils.

AIM
To use genome-wide transcriptome profiling in the blood of COPD patients to identify differences associated with the eosinophilic endotype.

METHODS
RNA-sequencing was performed using NextSeq in 40 COPD patients, 18% with blood eosinophilia (>300 eosinophils/mm³), and differential expression was analyzed using a standard bioinformatics pipeline.

RESULTS
The heatmap clearly differentiated eosinophilic (left hand-side panel) from non-eosinophilic (right) patients. Moreover, 38 genes showed at least a 1.5-fold increase (36 genes, including OLIG2, ALOX15, SIGLEC8, PRSS33, IL5RA & IDO1, all with Δ250-330%) or decrease (2 genes) in the expression of the eosinophilic group. Close to 50% of these genes had never been reported to be part of an eosinophil-related signature in asthma. Functional analysis was strongly associated with abnormal protein glycosylation (OR 73), being moderately associated with acetylcholine synthesis (OR 9), as well as with cell response to hypoxia, and regulation of either angiogenesis or lymphocytes and monocytes (OR 6, all). Moreover, seven of the upregulated genes were related to the latter ontology.

CONCLUSION
These results indicate that the eosinophilic endotype is associated with relevant changes in the transcriptomic profile of COPD patients. Part of these changes was unexpected on the basis of current knowledge and may have future therapeutic implications.
Prenatal exposure to organochlorine compounds and lung function until early adulthood

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Prenatal exposure to organochlorine compounds (OCs) increases the risk of adverse respiratory symptoms until adolescence, but evidence is mainly based on reported symptoms and it is still unknown whether these compounds can impact on lung function. We assessed the association between prenatal exposure to OCs and lung function until early adulthood.

We included 2622 participants from Menorca, Valencia, Gipuzkoa, and Sabadell belonging to the Infancia y Medio Ambiente birth cohort. Prenatal concentrations of OCs (hexachlorobenzene [HCB], dichlorodiphenyltrichloroethane [DDT], dichlorodiphenylchloroethylene [DDE], and polychlorinated biphenyls [PCB-118, -138, -153, -180]) were measured in maternal or cord serum. Lung function was measured by spirometry at 4, 7, 9, 11, 14, and 18 years of age.

High percentage of samples presented quantifiable levels of all measured OCs. Preliminary results in the Menorca cohort (n=327) revealed that prenatal exposure to the second tertile of PCB-153 concentrations was associated with reduced forced vital capacity (FVC) and reduced forced expiratory volume in 1 second (FEV1) when compared to the lowest tertile at 11 and 14 years (e.g. β for FVC at 14 years= -0.17 L; 95%CI= -0.31, -0.03). Exposure to the second tertile of DDE and PCB-118 was associated with reduced FVC at 11, compared to the lowest tertile. No other associations were found. Final results including all cohorts will be presented.

Preliminary results showed that prenatal exposure to OCs was associated with reduced lung function until adolescence. Such exposure might alter the structural development of the lung and predispose for chronic respiratory diseases later in life.
Analysis of hypoxia response factors (HIF) in chronic obstructive pulmonary disease (COPD) for the identification of non-invasive diagnostic biomarkers and prognosis

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Hypoxia is one of the main defining characteristics of chronic obstructive pulmonary disease (COPD), which causes lung tissue damage and an exaggerated inflammatory response at the pulmonary and systemic level. Hypoxia-inducing factors (HIF1, HIF2 and HIF3) are central regulators of cellular response to oxygen fluctuations. The role of HIF in COPD is quite unknown. Along this line recent data have shown that HIF2a is produces a hyperproliferation of bronchial epithelium in parallel with induction of soluble factors in the lung such as resistin-beta, which are localized in the bronchial epithelium and has been previously proposed as a bronchial epithelial mitogen.

We believe that HIF2-mediated response mechanisms may be the underlying molecular basis for the development of COPD, and that HIF2-dependent genes may be prognostic biomarkers for this pathology. To demonstrate this, we chose patients with COPD with severe and very severe obstruction (22 patients with respiratory failure-RI and 24 patients without RI) and as healthy controls 10 patients with normal lung function and no history of smoking. Demographic, clinical and comorbidities variables were collected and the expression of the Beta-resistin gene measured through the exhaled air condensate was analyzed.

Preliminary data from this study have observed that patients with COPD with RI have higher levels of expression of the resistin-beta compared to patients without IR. In addition, the expression of the resistin-beta in the control subjects is practically non-existent. In the group of COPD patients with RI, a significant, directly proportional relationship between the levels of resistin-beta expression and the degree of dyspnea, measured by the mMRC scale and the RV%, is observed.