ATP13A3 deficiency in human PAECs also resulted in an increase of endothelial monolayer permeability and an enhanced response to thrombin.

Conclusion *ATP13A3* is expressed in PAECs and plays a role in cell proliferation, apoptosis and endothelial permeability. These data provide initial insights into the pathogenicity of *ATP13A3* mutations in patients with PAH.

This work is produced by Prof. Nick Morrell's Group on behalf of the UK PAH Cohort Study.

S43 CIRCULATORY LEVELS OF MICRORNA-34A EXPRESSION IDENTIFY PATIENTS WITH POOR CLINICAL OUTCOME, AND REGULATE PULMONARY VASCULAR CELL PHENOTYPE

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Introduction Despite current therapies for pulmonary arterial hypertension (PAH), vascular endothelial dysfunction (endothelial-mesenchymal transition, EndoMT) along with hyperproliferative pulmonary vasculopathy persist. Circulatory microRNAs (miRs) offer considerable promise as both a prognostic biomarker, and to identify molecular mechanisms underlying PAH. Previous study from our lab identified whole blood miR-34a as downregulated in patients with PAH.

Aims 1) To assess and validate changes in circulatory miR-34a-5p and miR-34a-3p in patients with PAH, and 2) To investigate the role of miR-34a in pulmonary artery smooth muscle cells (PASMC) proliferation and in EndoMT of pulmonary artery endothelial cells (PAEC).

Methods The level of circulatory miR-34a expression was first measured using qRT-PCR in rodent animal models and age-sex matched healthy volunteers (HV) and IPAH patients from Sheffield, UK (plasma, HV, n=29, IPAH, n=27; whole blood, HV, n=11, IPAH, n=14), and then validated in another cohort from Beijing, China (plasma, HV, n=19, IPAH n=36; whole blood, HV=20, IPAH, n=39). The effect of miR-34a on cell proliferation, apoptosis, migration and endothelial-mesenchymal transition (EndoMT) were assessed in human PASMC and PAEC following transfection of either miR-34a-5p and miR-34a-3p mimics or antagonists, or scrambled miR.

Results Circulatory levels of miR-34a-5p and 3 p expression are downregulated in both IPAH patients and preclinical models of PAH. Reduced whole blood miR-34a-5p levels are associated with disease severity and poor survival. Transfection of PASMC with miR-34a-5p or −3 p antagonists promote PASMC proliferation and suppress apoptosis. In contrast, miR-34a-5p and −3 p mimics suppress PASMC proliferation and promote apoptosis. Transfection of PAEC with miR-34a-5p or −3 p mimics suppress EndoMT induced by combinatorial stimulation of TGF-beta1, IL-1beta and TNF-alpha, assessed by reduced EndoMT markers (alpha-SMA, Vimentin and Zeb1) and increased endothelial marker (VWF and CD31).

Conclusion This research identifies miR-34a as a key miR in the regulation of pulmonary vascular cell phenotype associated with the pathogenesis of PAH. Circulating levels of miR-34a could be a potential tool to stratify patients for treatments addressing PASMC proliferation and EndoMT. Further experiments in preclinical models are currently underway.

COPD: risk and prediction

S44 CHARACTERISTICS OF PATIENTS WITH RESPIRATORY SYMPTOMS BUT NO AIRFLOW OBSTRUCTION, IDENTIFIED AS PART OF THE ASSIST STUDY

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Aims In the United Kingdom, around 9 00 000 people have a formal diagnosis of COPD, however, it is believed that over 2 million more may be living with the disease. The ASSIST study (REC:16/5C/0629) aimed to investigate 'case finding' strategies in undiagnosed patients with histories and patterns of GP attendance suggestive of COPD.

Methods Possible cases were identified by applying a 'Read code' based electronic search algorithm based on previously reported medical record entries suggestive of COPD (Jordan et al, 2016), to GP practice records. The following algorithm variables were used: age, smoking status (ex and current smoker), history of dyspnoea (recorded in the previous 3 years), evidence of a prescription for salbutamol (and number of prescriptions) and evidence of a prescription for antibiotics.

These patients were then invited to their GP clinic for spirometry.

Results From the 2213 patients identified, 611 were excluded as ineligible by the GP, leaving 1601 invited to attend, from which 288 patients provided informed consent and attended. Of those, 76 (26.4%) had airflow obstruction ($FEV_1/FVC<0.7$) plus typical respiratory symptoms, indicating COPD. 156 (54.1%) had unobstructed lung function ($FEV_1/FVC\geq0.7$) but reported respiratory symptoms similar to those with newly identified COPD: dyspnoea (FEV1/FVC≥0.7 vs FEV1/FVC<0.7)(62.8% vs 55.2%, p=*0.34*) and cough (70.5% vs 68.4%, p=*0.85*). Patterns of co-morbidity between symptomatic patients with and without airflow obstruction were not significantly different for gastroesophageal reflux disease (GORD) (18.5% vs 10.5%, p=*0.14*), depression (26.2% vs 19.7%, p=*0.34*) or reported respiratory tract infections in the previous 12 months (27.5% vs 23.6%, p=*0.15*),but were for osteoarthritis (18.5% vs 6.5%, p=*0.02*), and obesity (BMI >29.9) (30.0 vs 28.5, p=*0.03*)

Conclusions Most patients identified by our electronic screening algorithm had significant respiratory symptoms, with approximately one quarter fulfilling COPD diagnostic criteria of post-bronchodilator FEV1/FVC<0.70, and a further half reporting a significant burden of respiratory

symptoms and chest infections despite lacking persistent airflow obstruction. Possible causes for respiratory symptoms in the unobstructed group include deconditioning, obesity, or early signs of airways disease. Further clinical characterisations and long term follow up would be recommended for this group of patients.

S45 PREDICTING LIKELIHOOD OF EMERGENCY DEPARTMENT ADMISSION PRIOR TO TRIAGE: UTILISING MACHINE LEARNING WITHIN A COPD COHORT

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Background Acute exacerbation of COPD is one of the commonest reasons for emergency department (ED) attendance and admission. Optimising ED patient flow requires early identification of patients needing inpatient care to initiate the admissions process, improve bed management and reduce ED length of stay. Stratifying COPD patients by likelihood of admission and length of stay at triage would potentially facilitate these and other operational efficiencies, such as targeting early supported discharge team review and COPD care bundle. We propose a machine learning (ML) based approach to predicting the need for admission from ED amongst a cohort of COPD patients.

Methods Retrospective cohort study utilising electronic health record (EHR) data from 13,173 ED encounters in 1,763 COPD patients who attended ED in our healthboard with diagnosis of COPD from April 1 st 2013 – March 31 st 2017. Utilising only variables obtained at patient registration or already in the EHR from prior visits, we developed predictive models using ML algorithms, specifically ensemble-based methods XGBoost and AdaBoost, to predict a patient's likelihood of admission during that ED encounter. Ten-fold cross-validation was used for model validation.

Results The overall admission rate was 68% (8,869 of 13 173 encounters). The AdaBoost model showed superior performance in the derivation of a COPD ED admission risk score, with precision (positive predictive value) of 0.83, recall (sensitivity) of 0.79, accuracy of 0.75, and an area under the receiver operating characteristic curve of 0.79. Precision, recall and negative predictive value improved with year of ED presentation, as data availability increased. The most significant features in the model included those related to prior utilisation of acute care services (both ED and inpatient).

Conclusions The use of ensemble ML algorithms to predict ED admissions utilising variables available at patient triage showed good performance. Such results highlight the ability of applied ML in the healthcare setting when incomplete and disordered data is expected. Adding prospective data is likely to further improve model accuracy. Surfacing actionable insights and decision support from ML-derived predictive models to clinicians in real-time, at point of care, offers prospects for optimising COPD management.

S46 BLOOD EOSINOPHIL COUNTS AND RISK OF SHORT-TERM HOSPITAL READMISSION FOR COPD EXACERBATION

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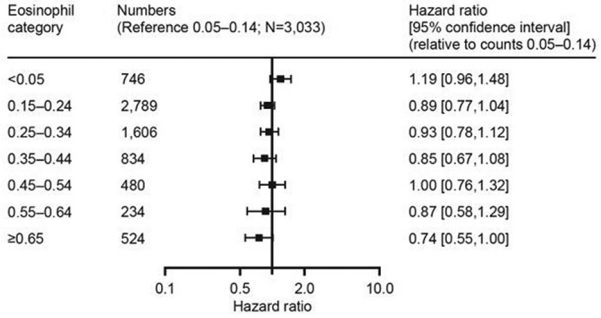
Introduction and objectives Elevated blood eosinophil count (BEC) is a proposed biomarker for risk of readmission for patients with COPD. We aimed to determine if preadmission BEC is an indicator of short-term hospital readmission for COPD exacerbation.

Methods We analyzed 2 years of medical records data (Clinical Practice Research Datalink with Hospital Episode Statistics linkage historic database) from patients hospitalized for COPD exacerbation (ICD-10 codes J44.0 or J44.1). Patients were included if they had a BEC recorded during stable disease (no exacerbation 4 weeks prior to measurement) within 1 year prior to hospitalization discharge (index date). We analyzed the association between BEC and readmission risk within 4 weeks after index date, with adjustment for age, sex, smoking status, body mass index, and timing of BEC by Cox regression. We also assessed independent clinical predictors of short-term hospital readmission.

Results Of 10 246 patients who met the inclusion criteria, 11.6% (n=1,189) were readmitted to hospital for COPD exacerbation within 4 weeks of discharge. Patients with very high BEC ($\geq 0.65\times10^9$/L; 5.1%) had the lowest risk (figure 1), which was most accentuated in 53% of patients treated with oral corticosteroids in general practice in the baseline year (hazard ratio [95% confidence interval]=0.53 [0.34–0.81]). A very low BEC ($<0.05\times10^9$/L) was a significant independent risk factor of short-term readmission, in addition to older age, male sex, being underweight, treatment with triple therapy, a greater number of baseline exacerbations, greater degree of dyspnea (modified Medical Research Council dyspnea scale score), lesser% predicted forced expiratory volume in 1 s, and a diagnosis of anxiety or depression.



COPD, chronic obstructive pulmonary disease.
Adjusted hazard ratios for readmission for COPD exacerbation within 4 weeks for patients assigned to ascending blood eosinophil count categories as compared with a reference blood eosinophil count 0.05–0.14x10^9/L.

Abstract 46 Figure 1 Short-term readmission for COPD exacerbations within 4 weeks