ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Pulmonary Hypertension in Eosinophilic *Versus* Non-Eosinophilic COPD

Bashar N. Alzghoul, Mohammad As Sayaideh, Brian F. Moreno, Saminder K. Singh, Ayoub Innabi, Raju Reddy, Eric S. Papierniak, Hassan M Alnuaimat

Please cite this article as: Alzghoul BN, As Sayaideh M, Moreno BF, *et al*. Pulmonary Hypertension in Eosinophilic *Versus* Non-Eosinophilic COPD. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00772-2020).

Title: Pulmonary Hypertension in Eosinophilic Versus Non-Eosinophilic COPD

Authors:

Bashar N. Alzghoul MD;[1,2 *] Mohammad As Sayaideh MD;[2] Brian F. Moreno MD;[2] Saminder K. Singh MD;[1,2] Ayoub Innabi MD;[1,2] Raju Reddy, MD;[1,2] Eric S. Papierniak, DO;[1,2] Hassan M Alnuaimat, MD[1,2]

Affiliations:

Division of Pulmonary, Critical Care and Sleep Medicine,[1] Department of Medicine,[2]
University of Florida, Gainesville, Florida, USA.

***Corresponding Author:** Bashar Alzghoul, MD

Mailing address: Bashar Alzghoul, M.D.
Division of Pulmonary, Critical Care and Sleep Medicine,
Department of Medicine, University of Florida
1600 SW Archer Road, Box 100277
Gainesville, Fl. 32610
Tel: 352.273-8734; fax: 352.273-9154
E-mail address: Bashar.alzghoul@medicine.ufl.edu

Take Home message

In COPD patients with right heart catheterization, eosinophilic COPD conferred a 7-fold increase in the likelihood of pulmonary hypertension and a 3-fold increase in the likelihood of pre-capillary pulmonary hypertension compared to non-eosinophilic COPD

Word Count: 2950

Abstract word count: 250

Number of tables: 5

Number of figures: 1

Short title: "Eosinophilic COPD and Pulmonary Hypertension"

Data availability

Data is available upon request from the corresponding author

Abstract

Background: Eosinophilic COPD phenotype is associated with greater airway remodeling, exacerbation risk, and steroid responsiveness. However, little is known about the prevalence and characteristics of pulmonary hypertension (PH) in this patient population.

Methods: We retrospectively evaluated a cohort of COPD patients with right heart catheterization (RHC) data at a university hospital between January 2011 and May 2019 and compared the pulmonary vascular profile and prevalence of PH between eosinophilic and non-eosinophilic patients using a definition of eosinophilic COPD as at least 3 blood eosinophil values ≥ 300 cells/µl. We used multivariable logistic regression analyses to examine the association between eosinophilic COPD and various PH categories adjusting for age, sex, body mass index, forced expiratory volume (%) in 1 second, smoking status, and use of supplemental oxygen.

Results: Among 106 COPD patients with RHC data and at least three blood eosinophil values, 25% met the definition of eosinophilic COPD. Fewer patients amongst the eosinophilic group required long term oxygen therapy (69% vs 93%, P=0.001) and total lung capacity was significantly lower in the eosinophilic group (P=0.006). This group had higher mPAP (median, (IQR); 30, (27-41) vs 25, (22-30) mmHg, P=0.001) and pulmonary vascular resistance (PVR) (4, (2.8-5.1) vs 2.9, (2.1-4.1) WU, P=0.018). On multivariable logistic regression analyses, eosinophilic phenotype was associated with PH (aOR= 6.5 (1.4-30.7), P=0.018), pre-capillary PH (aOR=3.2 (1.1-9), P=0.027) but not severe PH (aOR=2.1 (0.6-7.2), P=0.219).

Conclusion: Eosinophilic COPD was associated with higher mPAP, PVR and with increased likelihood of PH. More studies are needed to further explore this finding.

Key Words:

Cardiac catheterization

Eosinophils

Hypertension, pulmonary

Pulmonary disease, chronic obstructive

Pulmonary artery

Eosinophilic COPD

Abbreviation list

6-MWD= 6-minute-walk-distance; ATS= American Thoracic Society; BODE index= (body mass index, airflow obstruction, dyspnea and exercise) index; BMI= body mass index; CBC= complete blood count; CI= cardiac index; CLD-PH= pulmonary hypertension in chronic lung disease; CO= cardiac output; COPD= chronic obstructive pulmonary disease; CT=computed tomography; DLCO= diffusion capacity for carbon monoxide; ERS= European Respiratory Society; FEV1= forced expiratory volume (%) in 1 second; GOLD= Global Initiative for Chronic Obstructive Lung Disease; IQR= interquartile range; IL=interleukin; ILD= interstitial lung disease; mPAP= mean pulmonary artery pressure; NYHA= New York Heart Association functional classification; OR=odds ratio; PAH= pulmonary arterial hypertension; PCWP= pulmonary capillary wedge pressure; PFT= pulmonary function test; PH= pulmonary hypertension; PVR= pulmonary vascular resistance; RHC=right heart catheterization; RVSP= right ventricular systolic pressure; SD=standard deviation; TAPSE= tricuspid annular plane systolic excursion UF= university of Florida; WSPH= World Symposium on PH; WU= wood unit.

Introduction

Chronic obstructive pulmonary disease (COPD) is projected to be the third leading cause of death world-wide by 2030[1]. The presence of pulmonary hypertension (PH) in COPD has a stronger association with mortality as compared to pulmonary function test (PFT) parameters such as forced expiratory volume (%) in 1 second (FEV1%) or gas exchange variables[2, 3]. PH has been defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg but this has been revised in chronic lung disease patients (CLD-PH) into those with mPAP between 21-24 mmHg with pulmonary vascular resistance (PVR) ≥3 Wood units (WU) or mPAP ≥25 mmHg[3]. The prevalence of PH in COPD is probably underestimated as most data was derived from patients with severe disease undergoing lung transplant evaluation. Several studies have shown that up to 90% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV have mPAP >20 mmHg and approximately 5% of COPD patients have mPAP >35–40 mmHg at rest[3, 4].

Eosinophilic COPD has been increasingly recognized as a distinct phenotype. The 2019 GOLD report has introduced the blood eosinophil count as a biomarker to start or de-escalate inhaled corticosteroids[5]. Thresholds for eosinophilia assessed by different studies included relative eosinophil count of 2%, and absolute eosinophil counts of 150, 300, and 340 cells/μL[6]. Using a cutoff of 300 cells/μL, 20% of COPD patients were reported to have an eosinophilic phenotype[7]. The role of eosinophils in the development of pulmonary arterial hypertension (PAH) has been demonstrated in few animal[8–10] and human studies[11–13]. However, to our knowledge, no previous study has evaluated PH specifically in eosinophilic COPD patients.

Methods

We retrospectively evaluated a cohort of COPD patients who underwent RHC for evaluation of PH at the University of Florida (UF) between January 2011 and May 2019. We compared the pulmonary hemodynamic profile and prevalence of PH between patients with eosinophilic and non-eosinophilic COPD. Study was approved by UF institutional review board (IRB 201901525).

Study subjects and clinical variables

We initially identified 119 patients previously diagnosed with COPD who also had available RHC. The indication for RHC was either lung pre-transplant work-up or suspected PH. Information was collected about baseline characteristics, comorbidities, PFTs, echocardiogram, RHC, 6-minute-walking-distance (6-MWD), imaging and laboratory data. A board-certified pulmonary attending (HA) and a pulmonary fellow (BNA) reviewed the patients' chest computed tomography (CT) scans and PFTs and excluded patients who were mislabeled as COPD or had underlying interstitial lung disease (ILD). COPD was defined per the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[14]. One patient did not have spirometry available but had significant emphysema on chest CT and was included in the analysis[15]. Nine patients (previously labelled to have COPD but did not have any spirometric or radiologic evidence of COPD or had underlying ILD were excluded bringing the final number to 111 patients: 92 who underwent RHC for pre-transplant work-up and 19 for suspected PH. Vital signs were obtained on the day of RHC. Laboratory values closest to the RHC date were reported.

We classified the patients into eosinophilic vs non-eosinophilic COPD. Eosinophilia was defined as having at least 3 absolute blood eosinophil counts ≥ 300 cells/μl[5, 6, 16, 17]. We only included patients who had at least three separate complete blood count (CBC) results available (106 patients).

COPD severity parameters and pulmonary function test

Post bronchodilator spirometry, plethysmography, and diffusion capacity for carbon monoxide (DLCO) data was collected for each patient (Zan 500 Body, nSpire Health Inc, Louisville, Colorado, USA). These were performed according to ATS guidelines[18] using predicted values according to the third national health and nutrition examination survey[19]. PFT values were not available in 1 patient (0.9%). Patients were classified into four classes based on airflow limitation according to the GOLD 2020 report[5]. We also compared supplemental oxygen for each patient, smoking history, alpha-1 anti-trypsin deficiency, 6-MWD, BODE (body mass index,

airflow obstruction, dyspnea and exercise) COPD severity index, New York Heart Association functional classification (NYHA) and number of COPD exacerbations requiring hospitalization in the previous year.

Echocardiography

Transthoracic echocardiography was performed utilizing a Philips EPIQ 7 system (Philips Healthcare, Andover, MA, USA). We used echocardiographic values measured as described in the American Society of Echocardiography guidelines[20] as reported by board-certified cardiologists. The echocardiogram closest in time to the RHC was selected. The median time difference between obtaining the echocardiogram and RHC was 3 days (IQR 1-46).

Right heart catheterization

RHC was performed by a board-certified cardiologist or pulmonologist as part of the lung transplantation evaluation (82.9%) and/or if they had clinical suspicion for PH (17.1%). The majority of RHCs (90%) were performed as outpatient cases with no statistically significant difference between the two groups and only one patient in each group was being treated for COPD exacerbation when the RHC was performed. End-expiration values were recorded. Cardiac output (CO) was measured using either the thermodilution (74.8%) or indirect Fick method (25.2%)[21]. PVR was calculated as (mPAP-PCWP)/CO expressed in WU. Diastolic pulmonary gradient was calculated as the difference between the diastolic pulmonary artery pressure and PCWP[22]. We defined PH as mPAP ≥ 25 mmHg[2] and also reported the prevalence of PH as per the 2018 World Symposium on PH (WSPH) consensus definition of CLD-PH (mPAP between 21–24 mmHg with PVR ≥3 WU, or mPAP ≥25 mmHg) [3]. Pre-capillary PH was defined as mPAP ≥ 25 mmHg, PVR ≥3 WU and PCWP ≤ 15 mmHg, and severe PH as mPAP≥ 35 mmHg or 25-34 mmHg with cardiac index (CI) < 2 L/min/m^2 [3].

Sensitivity analysis

We performed a subgroup analysis comparing eosinophilic and non-eosinophilic COPD using only the pre-transplant cohort (92 patients). Additionally, we ran the analysis using an alternative definition of eosinophilic COPD as a single blood eosinophil count ≥ 340 cells/µl [23] (111 patients). Furthermore, using a definition of PH as mPAP ≥ 25 mmHg, we determined the prevalence of eosinophilia in those with and without PH.

Statistical analysis

We summarized the data as percentages for categorical variables, means ± standard deviation (SD) for normally distributed continuous variables and medians with interquartile range (IQR) for non-normally distributed continuous variables. Shapiro-Wilk test and visual inspection of variables' histograms were used to assess distribution normality. Independent sample T-test was used to compare variables with normal distribution and Mann-Whitney U test was used for variables with non-normal distribution. We constructed a clustered bar chart to demonstrate the prevalence rates of PH and its subgroups in eosinophilic versus non-eosinophilic COPD. We used multivariable logistic regression analyses to examine the association between eosinophilic COPD and various PH categories. In multi-variable models, we adjusted for age, sex, BMI[24], FEV1%, smoking status (active vs former) and need for supplementary oxygen during RHC which were chosen on a priori basis. We then presented the adjusted odds ratio (with 95% confidence intervals) of having various PH categories in eosinophilic versus non-eosinophilic. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (released 2015, IBM Corp, Armonk, NY).

Results

A total of 111 patients with confirmed diagnosis of COPD who also had RHC were identified, of which 106 had at least three CBC values were included in the primary analysis. Twenty-six patients (24.5%) met the definition of eosinophilic COPD. Both groups were generally middle-aged Caucasians and almost equally distributed between men and women (Table 1). Eosinophilic patients had higher BMI (P=0.006), more history of rheumatologic diseases (P=0.045) and were marginally more likely to have a history of

marijuana smoking and diabetes mellitus (P=0.052, 0.057, respectively). There were no significant differences in other comorbidities (Table 1).

There were no significant differences in FEV1% (median, IQR; 24 (19-48) vs 21 (17-26), P=0.101) or the GOLD airflow limitation severity. Fewer patients amongst the eosinophilic group required long term supplemental oxygen therapy (69% vs 93%, P=0.001). Furthermore, total lung capacity was significantly lower in the eosinophilic COPD group (P=0.006) (Table 2). There were no statistically significant differences between the two groups in the use of inhaled corticosteroids (77% vs 85%, P=0.341), chronic oral steroid therapy (23% vs 17.5%, P=0.528) or chronic azithromycin therapy (7.7% vs 10%, P= 0.727). Roflumilast use was more common in the eosinophilic COPD group but did not reach statistical significance (23% vs 10%, P=0.087). There was no statistically significant difference in any other COPD-related measured values (Table 2).

The reported echocardiographic parameters are summarized in Table 3. Eosinophilic COPD patients had more left atrial dilation (27% vs 10%, P=0.039) and marginally more left ventricular hypertrophy but did not reach statistical significance (P=0.059). There was no statistically significant difference in the other echocardiographic parameters. On RHC, the eosinophilic patients had higher systolic and diastolic pulmonary artery pressures (P=0.004 and 0.046 respectively), higher mPAP (30, (27-41) vs 25, (22-30) mmHg, P=0.001) and higher PVR (4, (2.8-5.1) vs 2.9, (2.1-4.1) WU, P=0.018). There was no statistically significant difference in PCWP, CO and CI (Table 3).

On univariable analysis, eosinophilic patients had more PH (OR, 95% CI; 8 (1.8-36.2), P=0.002), CLD-PH (per 2018 WSPH) (6.1 (1.3-27.8), P=0.01), pre-capillary PH (3.3 (1.3-8.3), P=0.01) and marginally more severe PH (2.5 (0.96-6.5), P=0.057) (Figure 1). On multivariable logistic regression adjusting for potential confounders, this phenotype was associated with PH (aOR= 6.9 (1.5-32.4), P=0.015) and pre-capillary PH (aOR=3.3 (1.2-9.1), P=0.023), but not with severe PH (aOR=1.7 (0.5-5.3), P=0.365) (Figure 2).

Using the same definition of eosinophilic COPD but including pre-transplant patients only, the eosinophilic group had higher mPAP (P=0.008) but not PVR (P=0.108). They also had more PH (89% vs 56%, P=0.011), CLD-PH (89% vs 62%, P=0.030) but not pre-capillary or severe PH (P=0.108 and 0.224, respectively) (Supplementary Table 1). Using a single eosinophil count of ≥ 340 cells/µl to define eosinophilic COPD, eosinophilic patients had higher mPAP (P=0.013) and PVR (P=0.047), more PH (P=0.016), CLD-PH (P=0.019), and pre-capillary PH (P=0.036) but not severe PH (P=0.164) (Supplementary Table 2). Comparing patients with and without PH, COPD-PH patients had higher blood eosinophil counts measured closest in time to the RHC (P=0.046), marginally higher maximum counts (P=0.050), and were more likely to have an eosinophilic phenotype using either definition (Table 5).

Discussion

In our study, eosinophilic COPD phenotype was associated with elevated mPAP and an increased likelihood of PH and pre-capillary PH compared to patients with non-eosinophilic COPD. On multivariable analyses adjusting for potential confounders, eosinophilic phenotype conferred a 7-fold increase in the likelihood of PH and a 3-fold increase in the likelihood of pre-capillary PH. In addition, one third of the patients with confirmed COPD-PH had eosinophilia as compared to 6% of the COPD-no PH group.

A growing body of evidence has identified eosinophilic COPD as a distinct phenotype[6, 25] and the use of peripheral eosinophilia as a biomarker to predict steroid responsiveness in COPD patients has been supported by several studies[7, 26–30]. Based on these findings, the GOLD guidelines recommend the use of an absolute eosinophil count ≥ 300 cells/µl as a cutoff to add or stop inhaled corticosteroids[5]. However, to our knowledge, this is the first study to investigate the pulmonary vascular hemodynamic profile of the eosinophilic COPD phenotype and its association with PH.

The previously reported prevalence of eosinophilic COPD ranges from around 20% to 70%, depending on the threshold used and the patient population studied[31]. In a post-hoc analysis of the WISDOM trial, 20% of the COPD patients had eosinophils ≥ 300 cells/µl[7] which is close to what we found in our study using the same cutoff (24.5%). However, we chose to use three eosinophil

counts as these tend to be unstable and using one measurement to define the eosinophilic COPD phenotype has been questioned before[6, 32]. The slightly higher BMI we found in our cohort is also similar to what has been reported in eosinophilic COPD, as is the similarity in GOLD airflow limitation between the two groups[31]. The eosinophilic patients had a significantly lower TLC, which could indicate that they had less hyperinflation and emphysema although we did not quantify the degree of emphysema on CT. This finding might also be in line with a report by Singh et al. who found that patients with persistent eosinophil counts <2% had more emphysema progression which is biologically plausible as neutrophils are known to cause more emphysema[26]. We chose not to include TLC in the multivariable model as it was unfortunately not available in a quarter of the patients. Lung hyperinflation is known to be associated with impaired left ventricular filling[33] and given that TLC values were generally lower in the eosinophilic group, including it in the model might have strengthened the association between eosinophilic COPD and PH.

Unlike asthma, the role of eosinophils in the pathophysiology of COPD is not fully clear[34], but they are associated with more airway remodeling and hyper-responsiveness[35]. The association we found between the eosinophilic COPD phenotype and PH is novel and remained significant despite adjusting for multiple confounders, using a different cutoff to define eosinophilia and limiting the analysis to the pre-transplant subgroup. Furthermore, patients with COPD-PH had higher blood eosinophil counts than COPD patients without PH. There is no reason to suspect that this finding was due to hypoxia as the eosinophilic group was less likely to require long term supplemental oxygen.

Although the eosinophilic patients had more left atrial dilation on echocardiogram, it is also unlikely that the difference in mPAP and PH prevalence was driven primarily by more pulmonary venous congestion as there was no difference in diastolic dysfunction on echocardiogram or PCWP on RHC. Additionally, pre-capillary PH was more prevalent in the eosinophilic COPD group. Of note, on subgroup analysis including pretransplant patients only, pre-capillary PH was numerically more in the eosinophilic COPD group but was not statistically significant (39% vs 21%, P=0.108). This could be due to the drop in sample size on subgroup analysis or that the difference in pre-capillary PH might be driven by non-transplant candidates.

There are few reports in humans linking eosinophils to PAH. A previous report from Sri Lanka found that more than 75% of patients with primary PAH had eosinophilia which was significantly higher than the control groups[11]. Similarly, in humans with Schistosomiasis-related PH, high levels of interleukin-5 (IL-5) and subsequent recruitment of eosinophils are thought to contribute to the development of PH[12]. In addition, there have been a handful of reports of PH associated with hypereosinophilic disorders.[36–38]. Finally, in a single center study from Germany, Harbaum et al. explored the CBC differential in patients with PAH and found that more than 50% had elevated blood eosinophils[13]. However, they used a much lower cutoff to define eosinophilia (≥ 100 cells/μl). Interestingly, the morphology of the vascular lesions noted in explanted lungs of patients with COPD-PH were comparable to those noted in idiopathic PAH in a report by Carlsen et al[39]. Whether eosinophils are biomarkers for PH or act as a direct vascular modulator in patients with PH is unclear. Daley et al. has previously shown that prolonged intermittent airway challenge with extrinsic antigens induced muscularization of small to medium-sized pulmonary arteries that was significantly ameliorated by the depletion of IL-13[8]. Furthermore, in a mouse model of PH, Weng et al. demonstrated that eosinophils were necessary to induce pulmonary vascular remodeling. Specifically, they compared the degree of pulmonary arterial muscularization in eosinophil deficient mice and wild type and found that eosinophil deficient mice have significantly less pulmonary arterial wall thickening. They also found that mice treated with anti-IL-5 antibodies had markedly lower BAL eosinophilia and more importantly, pulmonary arterial muscularization compared to mice treated with control antibodies. Additionally, the treatment of pulmonary arterial smooth muscle cells with eosinophilic granule extracts led to two-fold higher proliferation compared to the controls. They also found higher phosphorylation rates of protein kinase B (Akt) 1 and extracellular signal-regulated kinase (ERK) in these cells suggesting that the mechanism linking eosinophil and PH might be due to activation of Akt1 and ERK, both of which are downstream mediators of

pulmonary arterial smooth muscle cell proliferation [9]. In another animal model, anti-IL-5 effectively suppressed IL-33 induced pulmonary arterial hypertrophy[10]. Together, these studies suggest that eosinophils may contribute to the development of PH. However, it is more likely that the pathogenesis of PH in eosinophilic COPD is multifactorial as PH has not been reported in eosinophilic asthma, for example. We suspect that other processes such as chronic hypoxemia, respiratory acidosis, mechanical factors and loss of pulmonary vascular beds due to parenchymal destruction interact together to cause PH in COPD patients[4].

Our findings may have therapeutic implications, potentially opening the door to study the use of eosinophil-depleting biologics to treat or prevent PH in patients with eosinophilic COPD. In addition, screening for PH might be more warranted in patients with eosinophilic COPD but further research is needed. We acknowledge the limitations inherent in retrospective chart review studies. However, we meticulously reviewed the patients' charts and had strict inclusion criteria regarding COPD diagnosis, eosinophilic COPD definition and the need for RHC to define PH. Second, our study subjects were mainly Caucasians with severe and very severe COPD, hence the generalizability of our results to other races/ethnicities and to those with less severe disease might be limited. The severity of airway obstruction perhaps explains the low rate of bronchodilator response detected in our cohort even in eosinophilic COPD patients. Third, the referral bias perhaps explains the high prevalence of PH and severe PH in our patients. However, previous studies have shown that up to 90% of GOLD IV COPD patients can have mPAP >20 mmHg which close to our study[2–4]. Lastly, 17.5% of the non-eosinophilic COPD patients were on and off chronic oral prednisone therapy which could have caused falsely low eosinophil counts[40]. However, these patients were on low doses (≤ 10 mg daily), which have been shown to result in no or mild suppression of peripheral eosinophilia[41].

In summary, we found a significant association between eosinophilic COPD and PH. Patients with eosinophilic COPD had higher mPAP and PVR than non-eosinophilic COPD. More studies are needed to reproduce these results, investigate the pathophysiologic role of eosinophils in COPD-PH and to explore the role of eosinophil-depleting therapy in this patient population.

Author Disclosures:

None of the authors have conflict of interest

Author Contributions

BNA: study conception and design, project administration, IRB protocol preparation, statistical analysis, initial draft writing and manuscript reviewing and editing; BM: data collection, manuscript reviewing and editing; MA, SKS, AI: manuscript reviewing and editing; RR, ESP: supervision, study conception and design and manuscript review and editing; HA: study conception and design, study administration, supervision and manuscript reviewing and editing. BNA and HMA are the guarantors of the study. All authors reviewed and approved the final manuscript.

References

1. WHO | Global Health Estimates [Internet]. WHO World Health Organization; [cited 2020 Aug 31].Available from: http://www.who.int/healthinfo/global_burden_disease/en/.

2. Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, Marco TD, Galiè N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry J-L. Pulmonary Hypertension in Chronic Lung Diseases. *J. Am. Coll. Cardiol.* Journal of the American College of Cardiology; 2013; 62: D109–D116.

3. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur. Respir. J.* [Internet] European Respiratory Society; 2019 [cited 2020 May 26]; 53Available from: https://erj.ersjournals.com/content/53/1/1801914.

4. Chaouat A, Bugnet A-S, Kadaoui N, Schott R, Enache I, Ducoloné A, Ehrhart M, Kessler R, Weitzenblum E. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 2005; 172: 189–194.

5. Global Initiative for Chronic Obstructive Lung Disease [Internet]. Glob. Initiat. Chronic Obstr. Lung Dis. - GOLD [cited 2020 Aug 21].Available from: https://goldcopd.org/.

6. Harries TH, Rowland V, Corrigan CJ, Marshall IJ, McDonnell L, Prasad V, Schofield P, Armstrong D, White P. Blood eosinophil count, a marker of inhaled corticosteroid effectiveness in preventing COPD exacerbations in post-hoc RCT and observational studies: systematic review and meta-analysis. *Respir. Res*. 2020; 21: 3.

7. Watz H, Tetzlaff K, Wouters EFM, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PMA. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir. Med.* 2016; 4: 390–398.

8. Daley E, Emson C, Guignabert C, de Waal Malefyt R, Louten J, Kurup VP, Hogaboam C, Taraseviciene-Stewart L, Voelkel NF, Rabinovitch M, Grunig E, Grunig G. Pulmonary arterial remodeling induced by a Th2 immune response. *J. Exp. Med.* 2008; 205: 361–372.

9. Weng M, Baron DM, Bloch KD, Luster AD, Lee JJ, Medoff BD. Eosinophils are necessary for pulmonary arterial remodeling in a mouse model of eosinophilic inflammation-induced pulmonary hypertension. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 2011; 301: L927-936.

10. Ikutani M, Ogawa S, Yanagibashi T, Nagai T, Okada K, Furuichi Y, Takatsu K. Elimination of eosinophils using anti-IL-5 receptor alpha antibodies effectively suppresses IL-33-mediated pulmonary arterial hypertrophy. *Immunobiology* 2018; 223: 486–492.

11. Obeyesekere I, de Soysa N. "Primary" pulmonary hypertension, eosinophilia, and filariasis in Ceylon. *Br. Heart J.* 1970; 32: 524–536.

12. de Jesus AR, Silva A, Santana LB, Magalhães A, de Jesus AA, de Almeida RP, Rêgo MAV, Burattini MN, Pearce EJ, Carvalho EM. Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. *J. Infect. Dis.* 2002; 185: 98–105.

13. Harbaum L, Baaske KM, Simon M, Oqueka T, Sinning C, Glatzel A, Lüneburg N, Sydow K, Bokemeyer C, Klose H. Exploratory analysis of the neutrophil to lymphocyte ratio in patients with pulmonary arterial hypertension. *BMC Pulm. Med.* [Internet] 2017 [cited 2020 Aug 28]; 17Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405506/.

14. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, Calverley PMA, Chavannes N, Dillard T, Fahy B, Fein A, Heffner J, Lareau S, Meek P, Martinez F, McNicholas W, Muris J, Austegard E, Pauwels R, Rennard S, Rossi A, Siafakas N, Tiep B, Vestbo J, Wouters E, ZuWallack R. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur. Respir. J.* European Respiratory Society; 2004; 23: 932–946.

15. Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, Barr RG, Regan EA, Coxson HO, Hoffman EA, Newell JD, Curran-Everett D, Hogg JC, Crapo JD, Lynch DA, Kazerooni EA, Han MK. The Role of Chest Computed Tomography in the Evaluation and Management of the Patient with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* 2017; 196: 1372–1379.

16. Chapman KR, Hurst JR, Frent S-M, Larbig M, Fogel R, Guerin T, Banerji D, Patalano F, Goyal P, Pfister P, Kostikas K, Wedzicha JA. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am. J. Respir. Crit. Care Med.* American Thoracic Society - AJRCCM; 2018; 198: 329–339.

17. Yun JH, Lamb A, Chase R, Singh D, Parker MM, Saferali A, Vestbo J, Tal-Singer R, Castaldi PJ, Silverman EK, Hersh CP. Blood eosinophil thresholds and exacerbations in chronic obstructive pulmonary disease. *J. Allergy Clin. Immunol.* 2018; 141: 2037-2047.e10.

18. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, Hallstrand TS, Hankinson JL, Kaminsky DA, MacIntyre NR, McCormack MC, Rosenfeld M, Stanojevic S, Weiner DJ, ATS Committee on Proficiency Standards for Pulmonary Function Laboratories. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic Society Technical Statement. *Am. J. Respir. Crit. Care Med.* 2017; 196: 1463–1472.

19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am. J. Respir. Crit. Care Med.* 1999; 159: 179–187.

20. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of

Cardiology, and the Canadian Society of Echocardiography. *J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr.* 2010; 23: 685–713; quiz 786–788.

21. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. *Cardiovasc. Res.* 1970; 4: 23–30.

22. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest* 2013; 143: 758–766.

23. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am. J. Respir. Crit. Care Med.* 2016; 193: 965–974.

24. D'Andrea A, Naeije R, Grünig E, Caso P, D'Alto M, Di Palma E, Nunziata L, Riegler L, Scarafile R, Cocchia R, Vriz O, Citro R, Calabrò R, Russo MG, Bossone E. Echocardiography of the pulmonary circulation and right ventricular function: exploring the physiologic spectrum in 1,480 normal subjects. *Chest* 2014; 145: 1071–1078.

25. Tashkin DP, Wechsler ME. Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2018; 13: 335–349.

26. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R, ECLIPSE investigators. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur. Respir. J.* 2014; 44: 1697–1700.

27. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD. *Thorax* 2016; 71: 118–125.

28. Barnes NC, Sharma R, Lettis S, Calverley PMA. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur. Respir. J.* 2016; 47: 1374–1382.

29. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF, FLAME Investigators. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N. Engl. J. Med.* 2016; 374: 2222–2234.

30. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* 2015; 192: 523–525.

31. Wu H-X, Zhuo K-Q, Cheng D-Y. Prevalence and Baseline Clinical Characteristics of Eosinophilic Chronic Obstructive Pulmonary Disease: A Meta-Analysis and Systematic Review. *Front. Med.* [Internet] Frontiers; 2019 [cited 2020 Aug 21]; 6Available from: https://www.frontiersin.org/articles/10.3389/fmed.2019.00282/full.

32. Schumann DM, Tamm M, Kostikas K, Stolz D. Stability of the Blood Eosinophilic Phenotype in Stable and Exacerbated COPD. *Chest* 2019; 156: 456–465.

33. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, Magnussen H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. *Chest* 2010; 138: 32–38.

34. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir. Med.* 2017; 5: 747–759.

35. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. *Ther. Adv. Chronic Dis.* SAGE Publications; 2016; 7: 34–51.

36. Konno R, Tatebe S, Shirai T, Shimokawa H. Immunosuppressive therapy ameliorates refractory vasospastic angina, severe pulmonary hypertension, and bronchiolitis in a patient with eosinophilic granulomatosis with polyangiitis: a case report. *Eur. Heart J. Case Rep.* 2018; 2: yty050.

37. Ibe T, Wada H, Sakakura K, Ugata Y, Ito M, Umemoto T, Momomura S-I, Fujita H. A Case of Pulmonary Hypertension Associated with Idiopathic Hypereosinophilic Syndrome. *Int. Heart. J.* 2018; 59: 887–890.

38. Kawashima A, Kimura A, Katsuda S, Sumita R, Yachie A, Nonomura A, Nakanishi I. Pulmonary vasculitis with hypereosinophilia and episodic pulmonary hypertension: report of three siblings. *Pathol. Int.* 1995; 45: 66–74.

39. Carlsen J, Hasseriis Andersen K, Boesgaard S, Iversen M, Steinbrüchel D, Bøgelund Andersen C. Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *J. Heart Lung Transplant. Off. Publ. Int. Soc. Heart Transplant.* 2013; 32: 347–354.

40. Ortega H, Llanos J-P, Lafeuille M-H, Duh MS, Germain G, Lejeune D, Sama S, Bell C, Hahn B. Effects of systemic corticosteroids on blood eosinophil counts in asthma: real-world data. *J. Asthma Off. J. Assoc. Care Asthma* 2019; 56: 808–815.

41. Serra-Bonett N, Al Snih S, Rodriguez MA. Effect of Low-Dose Prednisone on Leukocyte Counts and Subpopulations in Patients With Rheumatoid Arthritis. *JCR J. Clin. Rheumatol.* 2009; 15: 148–149.

Table 1: Baseline demographics and clinical characteristics of eosinophilic COPD as compared to non-eosinophilic COPD[*]

	Eosinophilic COPD (N=26)	Non-Eosinophilic COPD (N=80)	P-Value
Demographics			
Age years (years ± SD)	64 ± 7.4	61.3 ± 7.7	0.124
Women, n (%)	12 (46.2)	45 (56.3)	0.370
Race, n/total n (%)			0.616
Caucasians	24 (92.3)	75/79 (94.9)	
African-Americans	2 (7.7)	4/79 (5.1)	
Clinical Characteristics			
Body mass index (kg/m^2 ± SD)	27 ± 4.3	24.3 ± 4.3	0.006
Heart rate (bpm ± SD) [†]	81.3 ± 15.5	80.8 ± 12.3	0.868
Oxygen saturation % (mean ± SD) [†]	96.3 ± 2.3	97.3 ± 2.7	0.093
Mean systemic blood pressure (mmHg ± SD) [†]	96.5 ± 14.4	99 ± 11.7	0.377
Marijuana use, n (%)	7 (26.9)	9 (11.3)	0.052
Asthma, n (%)	1 (3.8)	3 (3.8)	0.682
Atopic dermatitis, n (%)	3 (11.5)	3 (3.8)	0.156
Systemic hypertension, n (%)	14 (53.8)	44 (55)	0.918
Diabetes mellitus, n (%)	10 (38.5)	16 (20)	0.057
Congestive heart failure, n (%)	2 (7.7)	7 (8.8)	0.867
Obstructive sleep apnea, n (%)	4 (15.4)	9 (11.3)	0.577
Rheumatologic disease, n (%) [‡]	3 (11.5)	1 (1.3)	0.045
Laboratory findings[†]			
WBC *10^9 cells/L (mean ± SD)	8.5 ± 2.7	8.7 ± 3.6	0.820
PaO2 mmHg (IQR)[†]	83 (77-89)	80 (69-91)	0.541
Eosinophils cells/µl (mean ± SD)	333.5 ± 189.6	164.6 ± 70	<0.001
Brain natriuretic peptide pg/ml (IQR)	75.1 (16-184)	37.1 (20-122)	0.881

[*] Eosinophilic COPD was defined as having at least 3 separate absolute blood eosinophils count ≥ 300 cells/µl. Five patients did not have at least three eosinophil count values and were not classified based on this definition.

[†] Vital signs were reported on the day of right heart catheterization. Lab measures closest to the right heart catheterization date were reported. PaO2 on the RHC day was only available in 26% of the patients.

‡ Of the three patients in the eosinophilic group with rheumatologic disorders, one had rheumatoid arthritis with relapsing polychondritis (mPAP =40 mmHg), one had SLE (mPAP=32 mmHg) and one had scleroderma (mPAP=55 mmHg) and the one patient from the non-eosinophilic group had SLE (mPAP=21 mmHg). All of these 4 patients underwent RHC for PH evaluation and were not pretransplant patients.

COPD= chronic obstructive pulmonary disease; WBC= white blood cells

Table 2: COPD parameters and pulmonary function test data of eosinophilic COPD as compared to non-eosinophilic COPD[*]

	Eosinophilic COPD (N=26)	Non-Eosinophilic COPD (N=80)	P-value
Long term supplemental oxygen use, n/total n (%)	18 (69.2)	71/76 (93.4)	0.001
Supplemental oxygen during RHC, n/total n (%)	21 (81)	66/79 (83.5)	0.754
Active smoker, n (%)	0	2 (2.5)	0.416
Pack-year smoking amount, median (IQR)	36.8 (25-61.1)	40 (30-60)	0.390
Alpha-1 anti-trypsin deficiency, n/total n (%)	4/18 (22.2)	6/60 (10)	0.174
Six-minute walk distance, m (mean ± SD) [†]	226 ±102.9	240.6 ± 107.9	0.554
BODE index, median (IQR)[†]	6 (5-8)	7 (6-8)	0.104
NYHA class, median (IQR)[†]	3	3	0.074
COPD exacerbations in last year, median (IQR)[†]	1 (0-2)	1 (0-2)	0.784
Inhaled corticosteroids use, n (%)	20 (77)	68 (85)	0.341
Chronic azithromycin use, n (%)	2 (7.7)	8 (10)	0.727
Roflumilast use, n (%)	6 (23)	8 (10)	0.087
Chronic oral steroids use, n (%) [‡]	6 (23)	14 (17.5)	0.528
Pulmonary function test[†]			
FEV1% predicted, median (IQR)	24 (19-48)	21 (16.9-26.3)	0.101
FVC % predicted (mean ± SD)	56 ±16.9	53.2 ±17	0.454
FEV1/FVC %, median (IQR)	34 (28.1-60.5)	32 (26-39)	0.121
Positive bronchodilator response, n/total n (%)	1/23 (4.3)	6/65 (9.2)	0.457
TLC % predicted (mean ± SD)	96.5 ± 25.5	117.9 ± 27.2	0.006
DLCOHgb % predicted, median (IQR)	29.5 (20.3-46.3)	24.7 (18.5-34)	0.226
GOLD airflow limitation severity, n/total n (%)			
GOLD 1 ($FEV_1 \geq$ 80% predicted)	0	3/79 (3.8)	0.422
GOLD 2 (50% $\leq FEV_1 <$ 80% predicted)	6 (23.1)	4/79 (5.1)	0.007
GOLD 3 (30% $\leq FEV_1 <$ 50% predicted)	3 (11.5)	9/79 (11.4)	0.984
GOLD 4 ($FEV_1 <$ 30% predicted)	17 (65.4)	63/79 (79.7)	0.136

[*] Eosinophilic COPD was defined as having at least 3 separate absolute blood eosinophils count ≥ 300 cells/µl. Five patients did not have at least three eosinophil count values and were not classified based on this definition.

† Information regarding 6-minute walk distance, BODE index, NYHA and COPD exacerbations was available in 97.1%, 92.4%,94.3%, 62.2% of the patients respectively. Data regarding FEV1%, FVC and FEV1/FVC ratio were available in 99.2% of the patients. Data regarding TLC and DLCOHgb was available on 74.5% and 76.4% of the patients respectively.

‡ Oral prednisone doses ranged from 2.5 mg daily to 10 mg daily

COPD= chronic obstructive pulmonary disease; DLCOHgb= carbon monoxide diffusion capacity corrected for hemoglobin; FEV1= forced expiratory volume expired in the first second; FVC= forced vital capacity; NYHH= Ney-York heart association functional class; TLC= total lung capacity

Table 3: Echocardiographic parameters and right heart catheterization data of eosinophilic COPD as compared to non-eosinophilic COPD[*]

	Eosinophilic COPD (N=26)	Non-Eosinophilic COPD (N=80)	P-value
Echocardiogram			
Ejection fraction %, median (IQR)	60 (60-65)	65 (60-65)	0.193
Diastolic dysfunction, n/total n (%)	5/25 (20)	15/77 (19.5)	0.955
Left ventricular dilation, n (%)	1 (3.8)	1 (1.3)	0.398
Left ventricular hypertrophy, n (%)	3 (11.5)	2 (2.5)	0.059
Left atrial dilation, n/total n (%)	7 (26.9)	8/77 (10.4)	0.039
Right ventricular dilation, n (%)	8 (30.8)	22 (27.5)	0.748
Right ventricular hypertrophy, n/total n (%)	0	4 (5.1)	0.314
Right atrial dilation, n/total n (%)	5 (19.2)	14/75 (18.7)	0.949
RVSP, mmHg (mean ± SD)	56.7 ± 19.9	50.7 ± 24	0.473
Tricuspid regurgitation velocity, m/sec (mean ± SD)	3.5 ± 0.6	3.2 ±0.7	0.277
TAPSE mm, median (IQR)	20 (19-20)	20	0.789
Right heart catheterization parameters			
Systolic pulmonary artery pressure, mmHg (IQR)	45.5 (35.8-62.5)	37.5 (32-43.8)	0.004
Diastolic pulmonary artery pressure, mmHg (IQR)	20.5 (19.5-30.3)	20 (15-24.8)	0.046
Mean pulmonary artery pressure, mmHg (IQR)	30 (26.8-40.8)	25 (22-30)	0.001
PCWP, (mmHg ± SD)	14.7 ± 4.5	13 ± 4.3	0.096
Right atrial pressure, (mmHg ± SD)	10.2 ± 4.7	9.4 ± 3.8	0.353
Diastolic pulmonary gradient, mmHg (IQR)	10 (3-13.5)	5 (3-10)	0.064
Pulmonary vascular resistance, mmHg (IQR)	4 (2.8-5.1)	2.9 (2.1-4.1)	0.018
Cardiac output L/min (IQR)	4.3 (4-4.9)	4.2 (3.4-4.9)	0.394
Cardiac index L/min/m^2 (IQR)	2.4 (2.2-2.6)	2.2 (2-2.6)	0.760

[*] Eosinophilic COPD was defined as having at least 3 separate absolute blood eosinophils count ≥ 300 cells/µl. Five patients did not have at least three eosinophil count values and were not classified based on this definition.

IQR= interquartile range; PCWP= pulmonary capillary wedge pressure; RHC= right heart catheterization; RVSP= right ventricular systolic pressure; TAPSE= tricuspid annular plane systolic excursion; WSPH= world symposium on pulmonary hypertension

Table 4: Multivariable regression model assessing the association between eosinophilic COPD with pulmonary hypertension, pre-capillary pulmonary hypertension and severe pulmonary hypertension[*]

	Eosinophilic COPD (N=26)	Non-Eosinophilic COPD (N=80)	P-value	Adjusted P-value	Adjusted Odds ratio (95% CI)
Pulmonary hypertension, n (%) [†]	24 (92.3)	48 (60)	0.002	0.018	6.5 (1.4-30.7)
CLD-PH per the WSPH 2018, n (%) [†]	24 (92.3)	53 (66.3)	0.010	0.041	5.1 (1.1-23.9)
Pre-capillary pulmonary hypertension, n/total n (%) [†]	13 (50)	18/77 (23.4)	0.010	0.027	3.2 (1.1-9)
Severe pulmonary hypertension, n (%) [†]	10 (38.5)	16 (20)	0.057	0.219	2.1 (0.6-7.2)

[*] Eosinophilic COPD was defined as having at least 3 separate absolute blood eosinophils count ≥ 300 cells/µl. Five patients did not have at least three eosinophil count values and were not classified based on this definition. Regression model adjusted for age, sex, BMI, FEV1%, smoking status (active vs former) and the need for supplementary oxygen during right heart catheterization procedure.

† Pulmonary hypertension was defined as mPAP≥ 25 mmHg; pre-capillary pulmonary hypertension was defined as mPAP ≥ 25 plus PVR ≥ 3WU with PCWP ≤ 15. Severe pulmonary hypertension was defined as mPAP≥ 35 mmHg or mPAP 25-34 mmHg with cardiac index < 2 L/min/m^2. CLD-PH was defined per the 6th WSPH as mPAP between 21–24 mmHg with PVR ≥3 WU, or mPAP ≥25 mmHg.

CI= confidence interval; CLD-PH= chronic lung disease pulmonary hypertension

Table 5: Eosinophils count in patients with and without COPD-pulmonary hypertension*

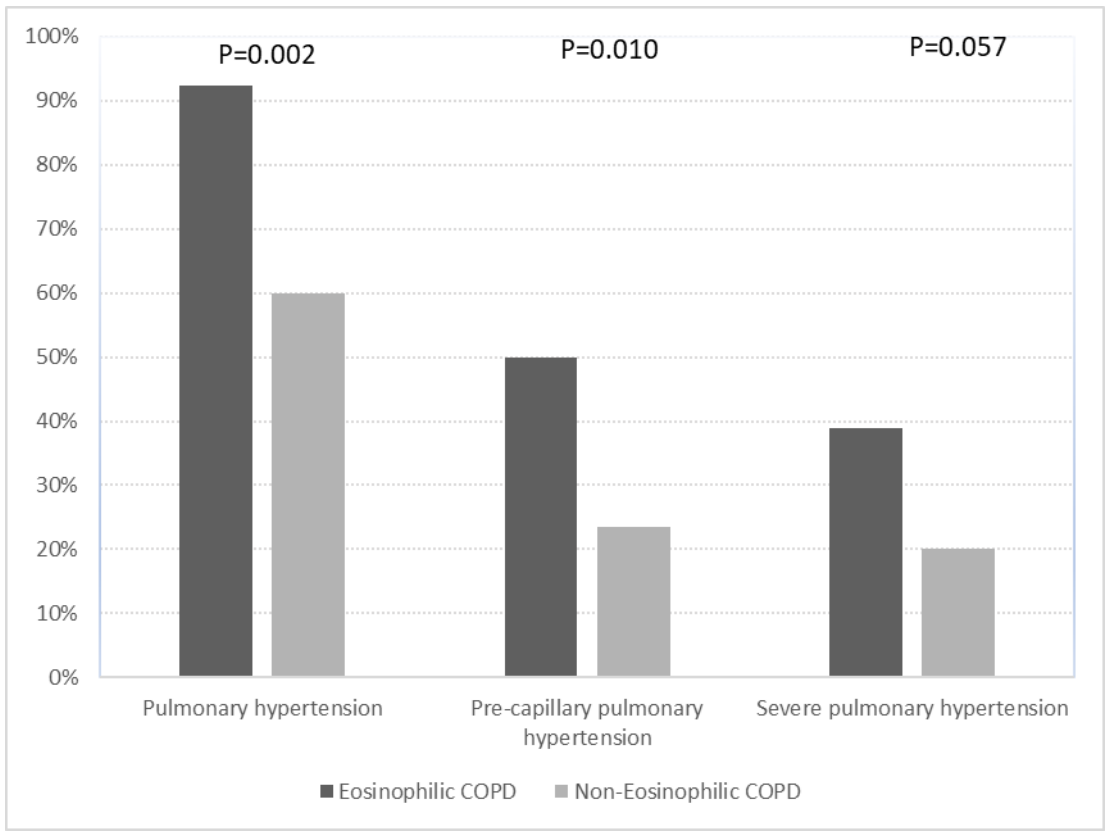
	COPD-PH (N=77)	COPD-no PH (N=34)	P-value
Max absolute blood Eos count, cells/µl (IQR)	263 (180-375)	220 (157-292.5)	0.050
Max blood Eos percentage, (IQR)	3.4 (2-5)	2.4 (2-4.1)	0.146
Eos absolute count closest to RHC, (IQR)	190 (140-270)	160 (117.5-230)	0.046
At least 3 Eos count ≥ 300 cells/µl, n/total n (%)	24/72 (33.3)	2/34 (5.9)	0.002
Max Eos count ≥ 340 cells/µl, n (%)	26 (33.8)	4 (11.8)	0.016

* Pulmonary hypertension was defined as hemodynamic measurement of mPAP≥ 25 mmHg

COPD= chronic obstructive pulmonary disease; Eos= eosinophils; max= maximum; mPAP= mean pulmonary artery pressure; RHC= right heart catheterization

Figure Legend:

Figure 1: Clustered-bar chart demonstrating the prevalence of pulmonary hypertension (PH), pre-capillary PH and severe PH in patients with eosinophilic COPD as compared to non-eosinophilic COPD patients.



Supplementary Table 1: Pulmonary hypertension in eosinophilic COPD vs non-eosinophilic COPD in pretransplant patients only[*] [†]

	Eosinophilic COPD (N=18)	Non-Eosinophilic COPD (N=71)	P-value
Right heart catheterization parameters			
Systolic pulmonary artery pressure, mmHg (IQR)	41 (35-50)	36 (31-40)	0.050
Diastolic pulmonary artery pressure, mmHg (IQR)	20 (17.5-25)	20 (15-22)	0.265
Mean pulmonary artery pressure, mmHg (IQR)	30 (25.8- 30.3)	25 (22-30)	0.008
PCWP, mmHg (mean ± SD)	14.7 ± 3.9	13 ± 4.3	0.143
Right atrial pressure, mmHg (mean ± SD)	9.8 ± 3.9	9 ± 3.6	0.427
Diastolic pulmonary gradient, mmHg (IQR)	6.5 (2.8-10)	5 (3-8)	0.550
Pulmonary vascular resistance, mmHg (IQR)	3.8 (2.5-4.2)	2.8 (2-3.6)	0.108
Cardiac output L/min (IQR)	4.1 (3.9-4.6)	4.2 (3.4-4.8)	0.880
Cardiac index L/min/m^2 (IQR)	2.5 (2.2-2.6)	2.2 (2-2.6)	0.601
Pulmonary hypertension, n (%) [†]	16 (88.9)	40 (56.3)	0.011
CLD-PH per the WSPH 2018, n (%) [†]	16 (88.9)	44 (62)	0.030
Pre-capillary pulmonary hypertension, n/total n (%) [†]	7 (38.9)	14/68 (20.6)	0.108
Severe pulmonary hypertension, n (%) [†]	4 (22.2)	8 (11.3)	0.224

[*] Eosinophilic COPD was defined as having at least 3 absolute blood eosinophils count ≥ 300 cells/µl

[†] Pulmonary hypertension was defined as mPAP≥ 25 mmHg; pre-capillary pulmonary hypertension was defined as mPAP ≥ 25 plus PVR ≥ 3WU with PCWP ≤ 15 mmHg. Severe pulmonary hypertension was defined as mPAP≥ 35 mmHg or mPAP 25-34 mmHg with cardiac index < 2 L/min/m^2. CLD-PH was defined per the 6th WSPH as mPAP between 21–24 mmHg with PVR ≥3 WU, or mPAP ≥25 mmHg.

CLD-PH= chronic lung disease pulmonary hypertension; COPD= chronic obstructive pulmonary disease; IQR= interquartile range; PCWP= pulmonary capillary wedge pressure; WSPH= world symposium on pulmonary hypertension

Supplementary Table 2: Pulmonary hypertension, pre-capillary pulmonary hypertension and severe pulmonary hypertension in eosinophilic COPD vs non-eosinophilic COPD patients using alternative definition of eosinophilic COPD [†]

	Eosinophilic COPD (N=30)	Non-Eosinophilic COPD (N=81)	P-value
Right heart catheterization parameters			
Systolic pulmonary artery pressure, mmHg (IQR)	45 (36.8-62.5)	38 (32-45)	0.007
Diastolic pulmonary artery pressure, mmHg (IQR)	20.5 (19.5-28.5)	20 (15-25)	0.133
Mean pulmonary artery pressure, mmHg (IQR)	30 (25.8-40.8)	25 (22-32)	0.013
PCWP, (mmHg ± SD)	14.5 ± 4.3	13.2 ± 4.3	0.149
Right atrial pressure, (mmHg ± SD)	10.3 ± 4.1	9.5 ± 4	0.393
Diastolic pulmonary gradient, mmHg (IQR)	9.5 (3-12.8)	6 (3-11.8)	0.383
Pulmonary vascular resistance, mmHg (IQR)	3.9 (2.6-5.1)	2.9	0.047
Cardiac output L/min (IQR)	4.1 (3.9-4.9)	4.2 (3.5-5.1)	0.652
Cardiac index L/min/m^2 (IQR)	2.2 (2-2.6)	2.2 (2.1-2.7)	0.150
Pulmonary hypertension, n (%) [†]	26 (86.7)	51 (63)	0.016
CLD-PH per the WSPH 2018, n (%) [†]	27 (90)	55 (67.9)	0.019
Pre-capillary pulmonary hypertension, n/total n (%) [†]	13/29 (44.8)	19/79 (24.1)	0.036
Severe pulmonary hypertension, n (%) [†]	11 (36.7)	19 (23.5)	0.164

[*] Eosinophilic COPD was defined as having maximum absolute blood eosinophils count ≥ 340 cells/µl

[†] Pulmonary hypertension was defined as mPAP≥ 25 mmHg; pre-capillary pulmonary hypertension was defined as mPAP ≥ 25 plus PVR ≥ 3WU with PCWP ≤ 15 mmHg. Severe pulmonary hypertension was defined as mPAP≥ 35 mmHg or mPAP 25-34 mmHg with cardiac index < 2 L/min/m^2. CLD-PH was defined per the 6th WSPH as mPAP between 21–24 mmHg with PVR ≥3 WU, or mPAP ≥25 mmHg.

CLD-PH= chronic lung disease pulmonary hypertension; COPD= chronic obstructive pulmonary disease; IQR= interquartile range; PCWP= pulmonary capillary wedge pressure; WSPH= world symposium on pulmonary hypertension