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TITLE OF THE MANUSCRIPT: Evaluation of Small Airway Function During COPD Exacerbation and Recovery Using Impulse Oscillometry (IOS) Device

SHORT TITLE: Impulse Oscillometry in COPD Exacerbation

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Conflict of interest

The authors acknowledge Chiesi Pharmaceuticals for the unconditional provision of iOS device. The company had no role in the design of the study, collection, analysis, or interpretation of data, or in writing the manuscript. The authors declare no conflicts of interest related to this manuscript. All authors have significantly contributed to the research and preparation of this manuscript and have no financial or personal relationships that could improperly influence or bias the presented work.

All authors contributed to data collection and/or analysis and critically reviewed the manuscript before submission.

Keywords: COPD, exacerbation, IOS, small airway

Abbreviations

• (ATS) The American Thoracic Society
• (AX) Reactance area
• (BORG) The Modified Borg Dyspnea Scale
• (CAT) The COPD Assessment Test
• (COPD) Chronic obstructive pulmonary disease
• (CRP) C-reactive protein
• (ECOPD) COPD exacerbations
• (ERS) The European Respiratory Society
• (FeNO) Fractional exhaled nitric oxide
• (FEV1) Forced expiratory volume in 1 second
• (Fres) Frequency response
• (FVC) Forced vital capacity
• (GOLD) Global Initiative for Obstructive Lung Disease
• (IOS) Impulse Oscillometry
• (MEF) Mean expiratory flow
• (mMRC) The modified Medical Research Council
• (PEF) Peak expiratory flow
• (PFTs) Pulmonary function tests
• (R5) Resistance at 5 Hz
• (R5−R20) Difference between resistance at 5 Hz and 20 Hz
• (R20) Resistance at 20 Hz
• (SAD) Small airway disease
• (SII) Systemic immune inflammation index
• (SIRI) Systemic inflammation response index
• (X5) Reactance at 5 Hz

Abstract

Background: Although recent guidelines emphasize objective criteria for assessing exacerbation severity, pulmonary function tests are still not included. This study aimed to evaluate small airway function during ECOPD and recovery periods using IOS.

Research questions: Can small airway function be assessed with IOS in ECOPD? Is there a relationship between IOS measurements and exacerbation severity? Is there an improvement in IOS measurements during the recovery period?

Study Design and Methods: In this prospective single-center study, patients with ECOPD underwent evaluation of their pulmonary functions using IOS and spirometry during exacerbation and recovery (6–12 weeks after exacerbation). The patients were divided into two groups: mild exacerbations and (moderate and severe) exacerbations based on ROME criteria.

Results: A total of 41 patients were initially enrolled, with 38 completing the study. At the onset of exacerbation, R5, R5-R20, X5, AX, and Fres were significantly correlated with FEV1%, and R5, R5-R20, AX, and Fres were also significantly correlated with the BORG score. Spirometry results were higher, while inflammation markers were lower in the mild exacerbation group. No differences in IOS parameters were observed based on exacerbation severity. Additionally, significant improvements were seen in CAT and BORG scores, FEV1%, FVC%, R5, R5-R20, AX, and Fres, along with a decrease in inflammation markers during the recovery period.

Interpretation: This study reveals several important and novel findings. IOS can be easily used in ECOPD, and IOS parameters that reflect small airways (R5–R20, AX, and Fres) are correlated with FEV1% and the severity of dyspnea. Additionally, IOS parameters significantly improve during recovery, except for R20. Further research is necessary on its application in the functional assessment of patients with COPD exacerbations.

Take-Home Points

Study Question

Can IOS measurements be used to evaluate pulmonary functions during COPD exacerbations?

Results

IOS measurements were easily applied to COPD patients during exacerbations. They showed a correlation with FEV1 and dyspnea at the onset of exacerbations, and there was a significant improvement in IOS measurements during recovery.

Interpretation

The IOS parameters, which reflect small airways, correlated better with FEV1 and dyspnea at the onset of an exacerbation and improved throughout recovery more than those of the large airway. This suggests that small airways are more affected during exacerbations, just as they are during stable periods.

Introduction

Exacerbations are the most common cause of morbidity and mortality in COPD. In the treatment of COPD, managing current exacerbations and preventing future ones are crucial.[1,2] Exacerbation of COPD (ECOPD) was defined as an acute worsening of respiratory symptoms that requires additional treatment. Its severity was evaluated based on the treatments administered or hospital admission.[3] This depended on patients' perception of symptoms, their self-management skills, or physicians' preferences for treatment of exacerbations, making it far from an objective measure. The definition of exacerbation in the Global Initiative for Obstructive Lung Disease (GOLD) 2023 report has been updated to reflect the Rome proposal, published in 2021.[1,4] A more detailed and objective definition was developed, incorporating respiratory findings and their duration, as well as etiology factors and related to pathogenesis, such as inflammation. Similarly, it was suggested that exacerbation severity should be determined according to more objective criteria, including clinical and laboratory findings.[1] However, pulmonary function tests (PFTs) have not been recommended by any guideline to define exacerbation or assess its severity in COPD to date.

On the other hand, the severity of asthma exacerbations has been assessed for many years based on objective criteria such as clinical and physical examination findings, peak expiratory flow (PEF) values, and oxygen saturation.[5] The complex maneuvers involved in spirometry often present challenges for elderly patients or those with impaired cognitive or neuromuscular functions, even during stable periods. Therefore, alternative PFTs to spirometry have been explored for many years in COPD patients. Impulse Oscillometry (IOS) is a simple, non-invasive, effort-independent method that uses sound waves to detect airway changes quickly. It only requires the patient to breathe normally to assess lung function by measuring both resistance and reactance of the airways.[6,7] These features of IOS suggest it may be a useful test for assessing patient respiratory function during exacerbation periods when airway resistance, airflow limitation, and respiratory muscle weakness further impair breathing.

We aimed to examine the parameters reflecting small airways during exacerbation using IOS, their relationship with clinical findings, exacerbation severity, and PFTs. We also compared the exacerbation measurements with those taken during recovery in the same patients.

Materials and Methods

Study design and setting

This single-center, prospective study was conducted at Medeniyet University Prof. Dr. Süleyman Yalçın Hospital in accordance with the Declaration of Helsinki. The study protocol received approval from the local institutional ethics committee (Date; No: 20.12.2023; 2023/0971), and written informed consent was obtained from all participants.

Study Population

Between March 2024 and September 2024, patients who were consecutively admitted to the emergency department or pulmonology outpatient clinic of our hospital with a diagnosis of ECOPD, as defined by the GOLD 2023 Report[1], were enrolled in the study. Patients diagnosed with pneumonia, pulmonary embolism, heart failure, pleural effusion, or pneumothorax were excluded. Additionally, patients who were unable to perform spirometry during exacerbation or had a forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of ≥ 0.70 were also excluded. The most common reasons for patient exclusion were the presence of pneumonia, inability to perform PFT, or an FEV1/FVC ratio ≥ 0.70. Patients were divided into two groups: mild exacerbations (group 1) and moderate and severe exacerbations (group 2) based on ROME criteria.[4]

Data Collection

The patients underwent IOS and PFT, along with completing questionnaires that included the case report form, the modified Medical Research Council (mMRC), the COPD Assessment Test (CAT), and the Modified Borg Dyspnea Scale (BORG). [8-10] PFT and IOS measurements were performed in all patients during both the acute exacerbation and the recovery period, which was defined as 6 to 12 weeks after the exacerbation. Relevant laboratory data, including complete blood counts and routine biochemical parameters, were retrospectively

documented from hospital records for further analysis. The systemic immune inflammation index (SII) and the systemic inflammation response index (SIRI) were calculated for each patient.[11,12]

IOS and Spirometry Measurements

Respiratory impedance was measured using a commercially available impulse oscillometry system (Jager, Germany; MS-IOS, V.5.72) following established protocols. Patients sat upright with their heads in a neutral position and were instructed to breathe normally through a mouthpiece connected to a pneumotachograph. A nose clip was used to prevent nasal airflow. To minimize upper airway shunting, patients supported their cheeks with their hands and kept their tongue and chin in a steady position throughout the procedure. Once stable tidal breathing was achieved, IOS measurements were recorded for at least 30 seconds. The test was repeated at least three times for each patient, and the measurement identified as a 'good test' by the oscillometry device was recorded as the patient's result. IOS measures three standard parameters for assessing airway resistance, including resistance at 5 Hz (R5), which indicates total airway resistance; resistance at 20 Hz (R20), representing the resistance of large airways; and the difference between resistance at 5 Hz and 20 Hz (R5-R20), which reflects resistance in small airways. The parameters that assess reactance are X5, which measures peripheral elastic resistance at 5 Hz; AX, the area under the reactance curve between 5 Hz and the resonant frequency, reflecting the elastic properties of the lung; and Fres, the oscillation frequency at which reactance is zero, helping to distinguish low-frequency from high-frequency reactance. Small airways dysfunction can be evaluated using R5-R20 along with X5, Fres, and AX. The data were analyzed following the European Respiratory Society (ERS) Task Force on forced oscillation technique testing.[13] After the IOS measurements, spirometry was performed according to the guidelines of the American Thoracic Society (ATS) and the ERS.[14] The FEV1%, FVC%, and FEV1/FVC ratio were recorded.

Statistical Analysis

Descriptive statistics for the numerical and categorical variables were calculated as median, 25th and 75th percentiles, number, and percentage frequencies. The Shapiro-Wilk test was used to check the normality assumption of the numerical characteristics, and it was

determined that they do not have a normal distribution. Differences between the mild exacerbation and moderate/severe exacerbation groups concerning numerical or categorical variables were examined using the Mann-Whitney U test or the Pearson chi-square test, respectively. The differences between exacerbation and recovery periods were evaluated by using the Wilcoxon Signed-Rank test. Correlations between numerical measurements were investigated using Spearman's Rank Correlation Analysis. Statistical significance was accepted as P<=0.05. SPSS (Version 29) was used for calculations.

Results

A total of 41 patients were initially enrolled. Among them, 38 completed the study because two experienced frequent exacerbations during the study, and one did not return for follow-up. Table 1 shows the clinical and laboratory characteristics of 41 patients at the onset of their exacerbation. FEV1% was correlated with all IOS parameters except R20, and BORG was correlated with IOS parameters except R20 and X5. Furthermore, IOS parameters reflecting the small airways (R5-R20, X5, AX, Fres) also showed strong intercorrelations. The p and r values for the correlations at the onset of exacerbation are shown in Table 2. The correlation between IOS measurements (absolute R5, R20, R5-R20, X5, AX, Fres) and FEV1% is illustrated in Figure 1, and their correlation with BORG is displayed in Figure 2. When patients were compared based on exacerbation severity, C-reactive protein (CRP) and SII, which are indicators of inflammation, were lower, while spirometry results (FEV1%, FVC%, and FEV1/FVC) were higher in Group 1. No difference was found between the groups regarding IOS parameters at the onset of exacerbation (Table 3).

Thirty-eight patients were re-evaluated during the recovery period. Significant improvements were observed in FEV1%, FVC%, R5, R5-R20, AX, and Fres, along with a decrease in CRP and inflammation indices (SII and SIRI) during recovery. Clinically, participants showed significant improvement in symptoms, as measured by the CAT and BORG scales. Comparison of clinical and functional characteristics of patients during exacerbation and recovery periods is provided in Table 4. The median and 25th and 75th quartiles of IOS measurements during the exacerbation and recovery periods are shown in Figure 3 using a box plot.

Disscussion

To our knowledge, this is the first study in the literature investigating changes in IOS parameters during exacerbation and recovery periods in COPD patients. We showed that at

the onset of exacerbation, R5, R5-R20, X5, AX, and Fres were significantly correlated with FEV1%, and R5, R5-R20, AX, and Fres were also significantly correlated with the BORG score. The resistance and reactance parameters of the IOS also showed a strong correlation with each other, besides the low correlation of R20 with X5 and Fres. At the onset of exacerbation, CRP and SII levels were lower in mild exacerbations, while FEV1%, FVC%, and FEV1/FVC ratios were higher. No differences were observed in IOS parameters based on the severity of exacerbation. Additionally, significant improvements were observed in FEV1%, FVC%, R5, R5-R20, AX, and Fres, along with a decrease in CRP, SII, and SIRI during recovery. Clinically, participants demonstrated notable improvement in symptoms, as measured by the CAT and BORG scales.

IOS Reproducibility

A key requirement for widespread use of PFTs in clinical practice is that they are consistent and reliable across different centers. One of the most significant findings of the ECLIPSE Study was the reliability of IOS parameters across continents.[15] In a prospective study of 94 COPD patients, changes in IOS measurements and FEV1% were monitored over one year in 58 patients. After this period, there were no statistically significant differences in the mean or median values of FEV1%, R5, X5, or Fres.[16] Another retrospective study showed that IOS resistance parameters demonstrate long-term reproducibility in both asthma and COPD. Additionally, the repeatability of spirometry parameters is lower than that of IOS resistance parameters across different GOLD stages.[17] Another important issue is the determination of cut-off values for these tests. A comprehensive review established practical IOS cutoff values for peripheral airway resistance in COPD as R5 > 0.5 kPa/L/s, R5-R20 > 0.10 kPa/L/s, and AX > 1.0 kPa/L.[18] In our study, the median values of R5 (0.51 kPa/L/s), R5-R20 (0.21 kPa/L/s), and AX (1.85 kPa/L/s) at the onset of exacerbation significantly exceeded these recommended thresholds. During recovery, although lower than during exacerbation, R5-R20 (0.17 kPa/L/s) and AX (1.51 kPa/L/s) still remained above these thresholds, with R5 at 0.42, just below the cutoff. Our results generally support the threshold values suggested in the review.

Small airway disease and its role in exacerbations

Small airway disease (SAD) is a key pathological feature that occurs early in COPD progression. In healthy individuals, the peripheral airways contribute minimally to overall airway resistance, whereas in patients with COPD, resistance in the peripheral airways increases significantly. [19, 20] Additionally, studies demonstrate that patients with COPD have

comparatively higher levels of small airway dysfunction than those with asthma and idiopathic pulmonary fibrosis. [21, 22]

Spirometry, commonly used for diagnosing and monitoring patients with COPD, falls short in assessing SAD. IOS, which has gained more widespread use in asthma and COPD in recent years, provides a more specific and comprehensive assessment of small airways, including resistance and reactance parameters. [23, 24] However, the ECLIPSE study showed no significant relationship between the presence of SAD and the R5-R20 and mean expiratory flow (MEF) values.[15]

Studies conducted so far have focused on the role of IOS measurements in early COPD diagnosis, their relationship with disease severity, and their role in predicting exacerbation risk. [15,18,23,24] We designed this study based on the assumption that small airway function would decline further during exacerbations. In the literature, studies on exacerbations and IOS are mainly found in the field of asthma, which suggests that damage to the peripheral airways could be a key factor in such asthma attacks. Additionally, while IOS alone was capable of predicting future exacerbations, fractional exhaled nitric oxide (FeNO), FEV1%, FEV1/FVC ratio, and bronchial hyperresponsiveness alone were not sufficient to predict exacerbations. [25,26,27] There are few studies in the literature examining the relationship between IOS parameters and exacerbation risk in COPD patients, which suggest that IOS parameters can be used to predict ECOPD. [24,28, 29] We performed IOS along with spirometry during both exacerbation and recovery periods in 38 patients. A key finding was that patients struggled or could not perform spirometry during exacerbations but could perform IOS with ease and in less time. We observed significant improvements in IOS parameters (R5, R5-R20, AX, and Fres), except for X5 and R20, as well as in FEV1%, FVC%, and the FEV1/FVC ratio during recovery compared to the onset of the exacerbation. Although there was no difference in median R20 values between exacerbation and recovery (0,29 vs 0,28), there was a significant decrease in median R5-R20 levels (0,21 vs 0,17). Our findings suggest that small airway resistance plays a more important role than large airway resistance during exacerbation, similar to the stable period in COPD patients. We can conclude that new medications and devices targeting the small airways are essential for treating COPD exacerbations.

Relationship of IOS measurements with exacerbation severity

To our knowledge, no studies in the literature have evaluated small airways using IOS during ECOPD. Several studies compare disease severity and IOS measurements in stable COPD. [15,29,30] The ECLIPSE cohort shows that R20 values are similar across GOLD stages 2-4, while R5-R20 values increase proportionally in these stages, suggesting that small airways mainly

contribute to the rise in lung resistance. [15] A study involving 215 stable COPD patients showed that IOS parameters, except R20, varied significantly with COPD severity, a finding similar to those in the ECLIPSE cohort. [29] Conversely, a retrospective observational study indicated that IOS parameters did not effectively differentiate stage 1 COPD patients from the general population or identify GOLD stage 3 and 4 patients among all COPD patients. [30] We compared individuals with mild exacerbations to those with moderate and severe exacerbations based on the ROME criteria. Significant differences were observed in spirometry results and inflammation markers according to exacerbation severity; FEV1%, FVC%, and FEV1/FVC ratios were higher, while CRP and SII were lower in the mild exacerbation group. We found no difference in IOS measurements between the two groups. The lack of differences in IOS parameters may be due to the small number of patients in our study.

Correlation between IOS and spirometry parameters at the onset of exacerbation

Many studies showed a significant correlation between IOS and spirometry parameters in patients with stable COPD.[16,29,31] In a prospective study of 94 COPD patients, R5, X5, and Fres were found to be significantly correlated with FEV1%. By measuring changes in FEV1% and IOS parameters in 58 patients after one year, it was observed that X5 was the only IOS measurement significantly correlated with FEV1% changes [14]. Similarly, in our study, at the onset of the ECOPD, the IOS measurement that had the strongest correlation with FEV1 was X5. A retrospective study found a stronger correlation between IOS and spirometry in COPD than in ACO across all severity levels.[31] A study comparing IOS measurements with spirometry parameters in patients with COPD observed a good correlation; reactance parameters showed a stronger correlation than resistance parameters.[29] We found that the IOS parameters measured at the onset of the ECOPD showed a significant correlation with the FEV1% value, except for R20. Additionally, aside from the weak correlation of R20 with X5 and Fres, the resistance and reactance parameters of IOS demonstrated a strong correlation with each other.

Correlation between IOS and respiratory symptoms at the onset of exacerbation

It is essential that PFTs used in COPD patients also relate to clinical features such as patients' complaints, quality of life, or mortality. In a study examining the relationships between IOS parameters and patient-reported outcomes in stable COPD, multiple regression analyses showed that R5-R20 or X5 most significantly explained the quality of life and dyspnea scores.[32] A study involving 768 COPD patients was conducted; small airway dysfunction, assessed by R5, R5–R20, X5, AX, and Fres, was linked to more severe respiratory symptoms

and a higher risk of ECOPD in previous years. Patients with IOS parameter abnormalities had higher mMRC and CAT scores.[28] However, a study analyzing data from 57 COPD patients found that mMRC did not correlate with IOS or spirometry.[33] While no correlation was found between IOS measurements and CAT and mMRC, a good correlation was observed between IOS parameters (R5, R5-R20, AX, Fres) and BORG in our study. Since BORG allows for the instantaneous assessment of dyspnea during exacerbations, it may better evaluate dyspnea and thus show a good correlation with IOS parameters. BORG can also be considered an alternative to the visual analog scale (VAS) in determining the severity of exacerbations.

Limitations

The primary limitation of our study is the small sample size. However, this is the first pilot study in the literature. Our strict adherence to the definition of exacerbation resulted to the exclusion of many patients from the study. Another limitation is that it is single-centered. Nonetheless, the strengths include its prospective design, performing IOS measurements during both exacerbation and recovery periods, and the consistency of our results throughout.

Interpretation

This study reveals several important and novel findings. IOS can be easily used in ECOPD. IOS parameters that reflect small airways (R5–R20, AX, and Fres) are correlated with FEV1% and the severity of dyspnea at the onset of an exacerbation. This correlation was not observed with R20, which represents large airways. No differences were observed in IOS measurements related to the severity of exacerbation. Additionally, IOS measurements significantly improve during recovery, except for R20. In conclusion, our results suggest that small airways are more affected than large airways during exacerbations, consistent with the findings during the stable period.

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Author contributions: E.E.Y. acts as guarantor for the content of this manuscript. E.E.Y., E.S.A.K., and B.A.Y. contributed to the conception and design of the study. D.K., E.H.K., D.B., and H.A. collected data. A.H. conducted data analysis and interpretation. E.E.Y. and E.S.A.K. drafted the manuscript. All authors contributed to data acquisition and/or interpretation and critically reviewed the manuscript before submission.

REFERENCES

1.Agustí A, Celli BR, Criner GJ et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Eur Respir J* 2023; 61(4):2300239.

2.Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370(9589): 786-796.

3. Vogelmeier CF, Criner GJ, Martinez FJ et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017; 195(5): 5575-82.

4. Celli BR, Fabbri LM, Aaron SD et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am J Respir Crit Care Me.* 2021;204 (11):1251-1258.

5. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. http://www.ginasthma.org. Date last updated: August 26 2025. Date last accessed: August 26 2025.

6. Dubois AB , Brody AW , Lewis DH et al. Oscillation mechanics of lungs and chest in man . *J Appl Physiol* 1956; 8(6) : 587 – 594.

7. Komarow HD , Myles IA , Uzzaman A et al. Impulse oscil lometry in the evaluation of diseases of the airways in children . *Ann Allergy Asthma Immunol* 2011;106(3): 191 – 199.

8. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54(7):581–586.

9. Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD assessment test. *Eur Respir J* 2009;34(3):648–654.

10. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14 (5)377−381.

11. Xu Y, Yan Z, Li K, Liu L. The association between systemic immune-inflammation index and chronic obstructive pulmonary disease in adults aged 40 years and above in the United States: a cross-sectional study based on the NHANES 2013-2020. *Front Med (Lausanne)*. 2023;10:1270368.

12. Chen Y, Pei Y, Mo W, Wang H. The Relationship Between Serum Inflammatory Markers and Chronic Obstructive Pulmonary Disease in Middle-Aged and Older Adults in the United States: A Cross-Sectional Study Based on NHANES 2013-2018. *Int J Chron Obstruct Pulmon Dis*. 2025;20:2837-2846.

13. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. ERS task force. *Eur Respir J* 2003;22(6):1026-1041.

14. M.R. Miller, R. Crapo et al, ATS/ERS Task Force, General considerations for lung function testing, *Eur. Respir. J* 2005; 26(1): 153–161.

15. C Crim, B. Celli, L.D. Edwards, et al. Investigators, Respiratory system impedance with impulse os- cillometry in healthy and COPD subjects: ECLIPSE baseline results, *Respir. Med* 2011; 105(7): 1069–1078.

16. Kolsum U, Borrill Z, Roy K, et al. Impulse oscillometry in COPD: identification of measurements related to airway obstruction, airway conductance and lung volumes. *Respir Med.* 2009;103(1): 136-143.

17. Xu J, Sun X, Zhu H, et al. Long-term variability of impulse oscillometry and spirometry in stable COPD and asthma. *Respir Res* 2022 ;23(1):262.

18. Lipworth BJ, Jabbal S. What can we learn about COPD from impulse oscillometry? *Respir Med* 2018;139:106-109.

19. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278(25):1355-1360.

20. Yanai M, Sekizawa K, Ohrui T, et al. Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure. *J Appl Physiol* 1992;72(3):1016-1023.

21. P.A. Williamson, K. Clearie, D. Menzies, et al. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD, *Lung* 2011; 189 (2): 121–129.

22. Duman D, Taştı ÖF, Merve Tepetam F. Assessment of small airway dysfunction by impulse oscillometry (IOS) in COPD and IPF patients. *Eur Rev Med Pharmacol Sci* 2023; 27 (7):3033-3044.

23. Su ZQ, Guan WJ, Li SY, et al. Si gnificances of spirometry and impulse oscillometry for detecting small airway disorders assessed with endobronchial optical coherence tomography in COPD. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 3031-3044.

24. Park H, Lee HJ, Lee HW, et al. Diagnosis and evaluation of small airway disease and COPD using impulse oscillometry. *Sci Rep* 2024;14(1): 28030.

25. Ling Y, Si M, Niu Y, et al. The predictive value of impulse oscillometry for asthma exacerbations in childhood: A systematic review and meta-analyses. *Pediatr Pulmonol* 2021;56(7):1850-1856.
26. Schulze J, Biedebach S, Christmann M, et al. Impulse Oscillometry as a Predictor of Asthma Exacerbations in Young Children. *Respiration* 2016; 91(2):107-114.
27. Zheng S, Hu Y, Chen Z, et al. Predicting asthma ex acerbation by impulse oscillometry evaluation of small airway function and fractional exhaled nitric oxide in preschool children. *Pediatr Pulmonol* 2020; 55(7):1601-1607.
28. Lu L, Peng J, Wu F, et al. Clinical characteristics of airway impairment assessed by impulse oscillometry in patients with chronic obstructive pulmonary disease: findings from the ECOPD study in China. *BMC Pulm Med* 2023;23(1):52.
29. Wei X, Shi Z, Cui Y, et al. Impulse oscillometry system as an alternative diagnostic method for chronic obstructive pulmonary disease. *Medicine (Baltimore*). 2017;96(46):e8543.
30. Gao L, Wang H, Wu Y, et al. Diagnostic value of impulse oscillometry in chronic obstructive pulmonary disease: a multicentre, retrospective, observational study. *BMJ Open* 2024;14(10):e087687.
31. Huang Y, Zhang X, Wang J, et al. Role of impulse oscillometry in chronic obstructive pulmonary disease and asthma-chronic obstructive pulmonary disease overlap. *Clin Transl Allergy* 2025;15(4):e70057.
32. Haruna, A., Oga, T., Muro, S. et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med* 2010; 10:10.
33. Anderson WJ, Lipworth BJ. Relationships between impulse oscillometry, spirometry and dyspnoea in COPD. *J R Coll Physicians* Edinb 2012; 42(2): 111-115.

Table 1: Clinical and laboratory characteristics of the patients at the onset of the exacerbation (n=41)

Variables	Median (25th-75th) or n (%)
Age (years)	66,0 (58,0-71.5)
Gender, male	31 (75.6)
BMI (kg/m^2)	26,0 (23,4-29,8)
Smoking (package-year)	40,0 (30,0-50,0)
Duration of COPD diagnosis (years)	6,00 (1,00-17,50)
Percentage of patients with frequent exacerbations	%75,6
CAT score	22,0 (11,0-29,5)
BORG score	5,00 (3,00-6,00)
Percentage of patients with VAS score<5	%61,0
SatO2 (%)	94,0 (91,0-96,0)
FEV_1%	43,0 (34,5-58,5)
FVC %	62,0 (47,5-76,0)
FEV_1/FVC	60,0 (50,6-66,7)
R5 (kPa/L/s)	0,54 (0,40-0,68)
R20 (kPa/L/s)	0,29 (0,24-0,34)
R5-R20 (kPa/L/s)	0,21 (0,13-0,32)
X5 (kPa/L/s)	-0,19 (-0,35- -0,12)
AX (kPa/L)	1,98 (0,92-3,24)
FRes (Hz)	23,8 (18,2-27,8)
CRP	3,9 (1,3-20,5)
NLR	3,15 (2,15-10,99)
Number of eosinophils	240,0 (95,0- 445,0)
Percentage of eosinophils	2,70 (0,95-4,55)
SII	818497,0 (550943,5- 1361526,0)
SIRI	7,1 (1,9- 206,4)

Abbreviations: BMI: Body mass index, CAT: COPD Assessment Test, BORG: the Modified Borg Dyspnea Scale, VAS: Visual analog scale, $SatO_2$:peripheral oxygen saturation measured by pulse oximetry, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEV1/FVC: ratio of FEV1 to FVC, R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Area of low-frequency reactance, Fres: Frequency response, CRP: C-reactive Protein, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index

Table 2: The correlation between IOS measurements with each other, spirometric parameters, and BORG dyspnea scale in patients at the onset of the exacerbation

	FEV1 %	FVC %	FEV1/FVC	BORG	R5	R20	R5-R20	X5	AX	Fres
R5	-.366*	-.405**	-,104	-,316*	--	,811***	,924***	-,645***	,896***	,647***
R20	-,290	-,405**	-,016	,061	,811***	--	,559***	-,390*	,583***	,437*
R5-R20	-,325*	-,295	-,117	,411**	,924***	,559***	--	-,695***	,948***	,662***
X5	,461*	,385*	,261	-,255	-,645***	-,390*	-,695***	--	-,840***	-,580***
AX	-,366*	-,335*	-,169	,369*	,896***	,583***	,948***	-,840***	--	,762***
Fres	-,368*	-,311*	-,240	,378*	,647***	,437*	,662***	-,580***	,762***	--

P value< 0.05*, P value< 0.01 **, P value< 0.001***

Abbreviations: R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Reactance area, Fres: Frequency response, FEV1: Forced expiratory volume in one second

Table 3: Comparison of clinical and functional characteristics of patients based on ROME classification at the onset of the exacerbation (n=41)

Variables	Mild exacerbation (n=26)	Moderate and severe exacerbation (n=15)	P
	median (25th-75th) or n (%)		
Age (years)	66(55-70)	66(59-73)	0,515
Gender, male	%61,3	%38,7	0,619
BMI (kg/m^2)	25,6 (23,3-29,1)	26,6(23,4-34,5)	0,465
Smoking (package-year)	40(30-48)	45(30-55)	0,222
Duration of COPD diagnosis (years)	6 (2-18)	4 (1-15)	0,505
Number of exacerbations in the previous year	2,5 (1-4)	3 (0-5)	0,701
CAT score	20 (11-28)	27 (11-34)	0,357
BORG score	5 (3-6)	5(3-7)	0,538
VAS score<5	%88	%12	**0,01**
SatO2 (%)	95 (93-96)	90 (84-95)	**0,005**
FEV_1%	49,5 (38-66)	35(24-46)	**0,002**
FVC %	70 (54-78)	51 (34-65)	**0,006**
FEV_1/FVC	62,7(55,7-67)	52,6 (46,6-61,2)	**0,050**
R5 (kPa/L/s)	0,51 (0,39-0,72)	0,55 (0,41-0,65)	0,807
R20 (kPa/L/s)	0,27 (0,24-0,32)	0,31 (0,28-0,36)	0,184
R5-R20(kPa/L/s)	0,22 (0,15-0,36)	0,21 (0,11-0,29)	0,379
X5 (kPa/L/s)	-0,19 (-0,35- -0,13)	-0,19 (-0,35- -0,11)	0,860
AX (kPa/L)	1,94 (0,93-3,37)	1,98 (0,88-3,10)	0,808
FRes (Hz)	23,75(18,36-27,48)	24,22 (16,88-28,20)	1,000
CRP	3 (1-9)	20 (2-61)	**0,041**
Number of eosinophils	265(160-460)	160(10-430)	0,113
percentage of eosinophils	2,85 (1,5-4,8)	1,70(0,1-3,5)	**0,044**
SII	742876,5 (449261-1044047)	1256520 (744230- 1496205)	**0,015**
SIRI	9,10 (1,53-170,4)	7,14 (2,04-242,3)	0,823

Abbreviations: BMI: Body mass index, CAT: COPD assessment test, BORG: Modified Borg dyspnea scale, VAS: Visual analog scale, SpO_2:peripheral oxygen saturation measured by pulse oximetry, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEV1/FVC: Ratio of FEV1 to FVC, R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Area of low-frequency reactance, Fres: Frequency response, CRP: C-reactive protein.

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Table 4: Comparison of clinical and functional characteristics of patients exacerbation and recovery periods

Variables	Exacerbation median (25th-75th)	Recovery median (25th-75th)	P
FEV_1%	43,0 (35,0- 59,0)	47,0 (39,0-75,0)	**0,001**
FVC %	62,0 (48,0-76,0)	66,0 (49,0-81,0)	**0,045**
FEV_1/FVC	60,3 (51,6- 66,8)	63,0 (50,7-73,7)	**0,017**
R5 (kPa/L/s)	0,51(0,39-0,66)	0,42 (0,35-0,56)	**0,040**
R20	0,29 (0,24-0,34)	0,28 (0,24-0,31)	0.793
R5-R20 (kPa/L/s)	0,21 (0,13-0,32)	0,17 (0,10-0,23)	**0,024**
X5 (kPa/L/s)	-0,18 (-0,33- -0,12)	-0,17 (-0,25- -0,10)	0,593
AX (kPa/L/s)	1,85 (0,90-3,17)	1,51 (0,57- 2,57)	**0,050**
FRes (Hz)	23,8 (18,0-27,7)	19,9 (16,3-23,9)	**0,013**
CAT score	22,0 (11,0-29,0)	13,0 (6,0-20,0)	0,001
BORG score	5,00 (3,00-6,00)	1,00 (0-3,00)	0,001
CRP	3,92 (1,23-20,90)	2,26 (1,21-4,55)	**0,014**
NLR	3,15 (2,15-12,21)	2,00 (2,00-3,00)	**0,001**
Number of eosinophils	250,0 (147,5-465,0)	220,0 (160,0-320,0)	0,187
Eosinophils %	2,70 (1,10-4,63)	3,00 (2,05- 3,95)	0,919
SII	813880 (550943,5-1361526)	637813(434617- 832727,5)	**0,004**
SIRI	5,92 (1,90-137,69)	699,3 (509,8- 1172,4)	**0,001**

Abbreviations; FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEV1/FVC: ratio of FEV1 to FVC, R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Area of low-frequency reactance, Fres: Frequency response, CAT: COPD assessment test, BORG: Modified Borg dyspnea scale, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index.

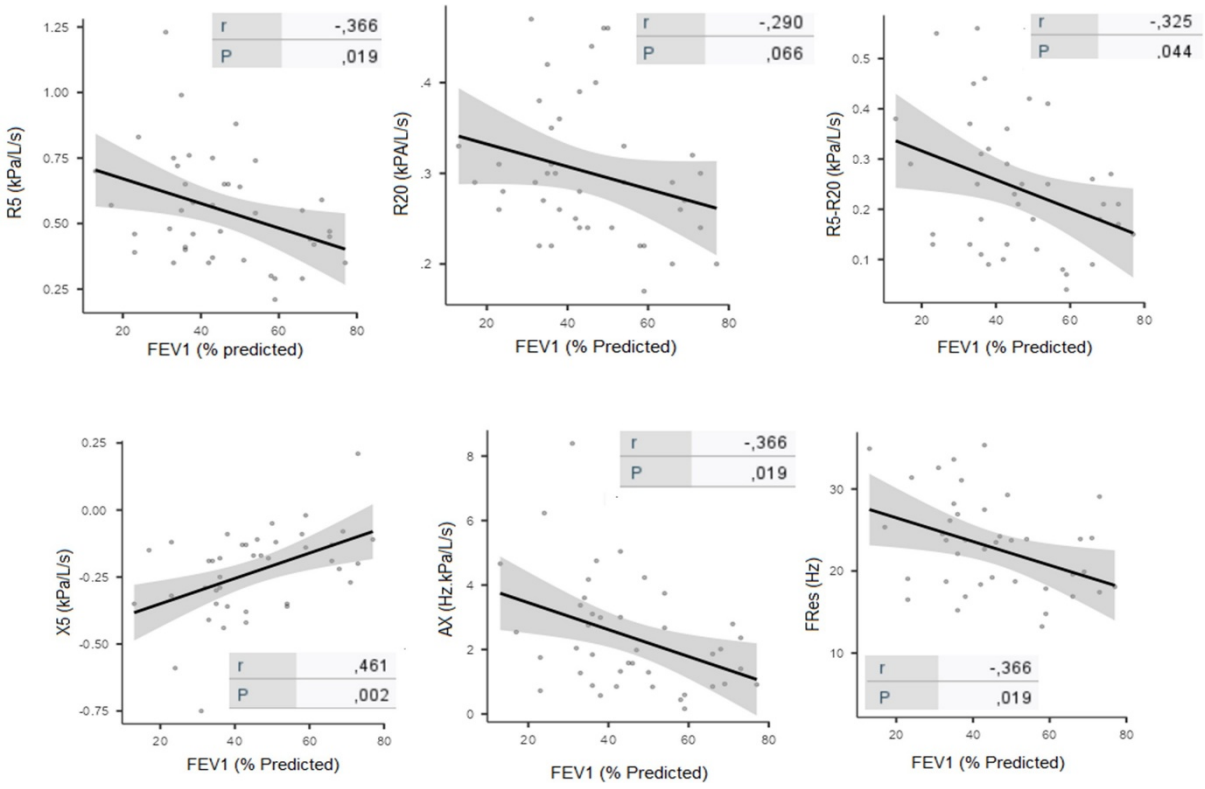

Figure 1. Correlation between IOS parameters and FEV1% at the onset of exacerbation. FEV1: Forced expiratory volume in one second, R5: Resistance at 5 Hz, R20: Resistance at 20, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Reactance area, Fres: Frequency response (n=41).

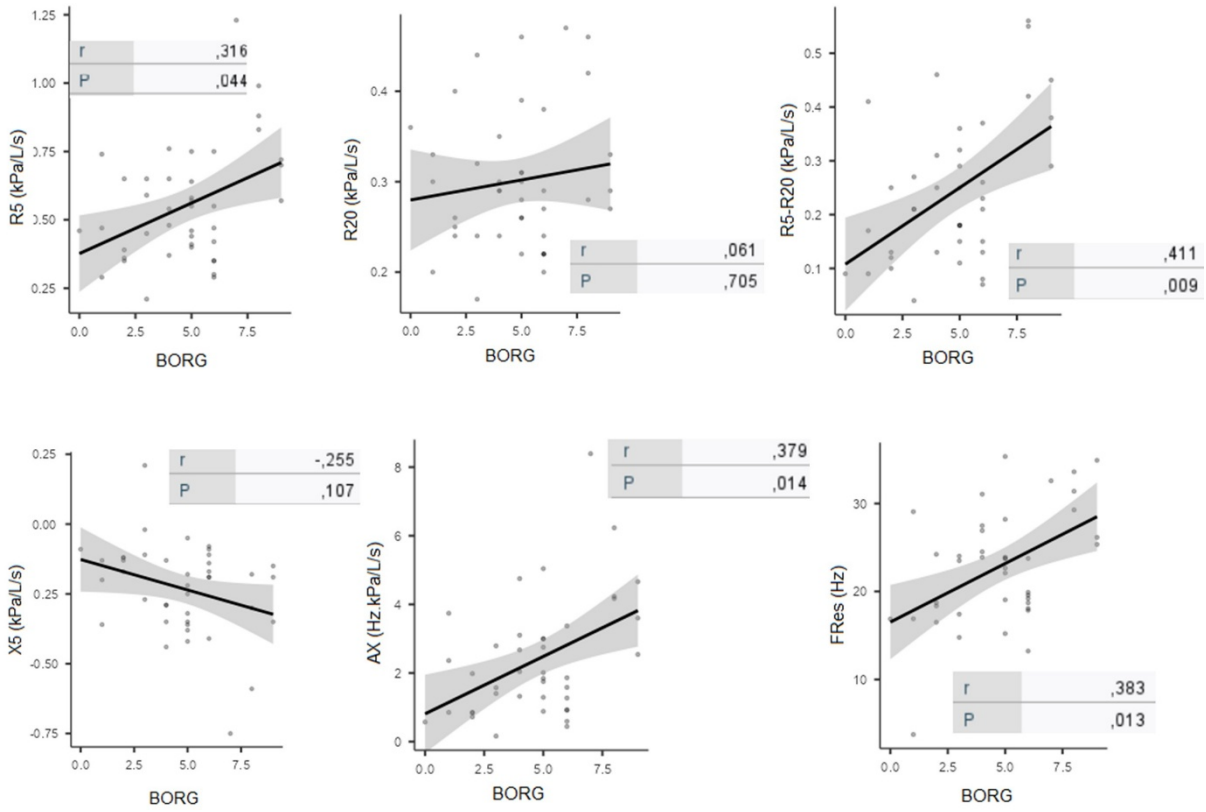

Figure 2. Correlation between IOS parameters and BORG score at the onset of exacerbation BORG: Modified Borg dyspnea scale, R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Reactance area, Fres: Frequency response (n=41).

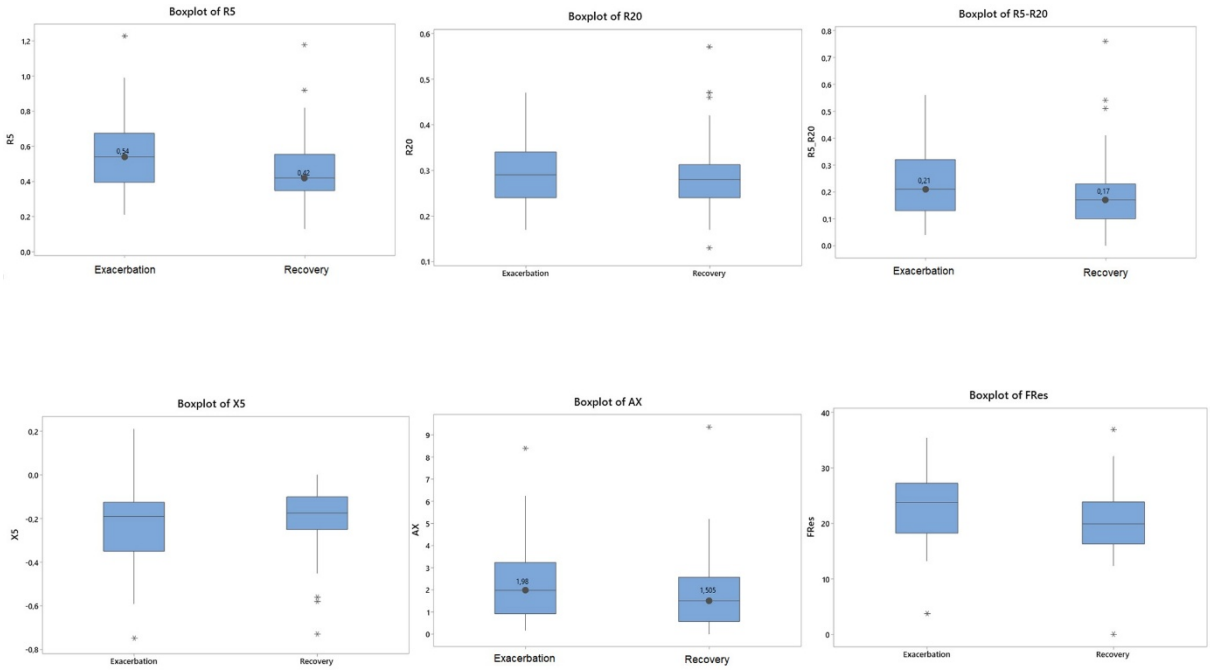

Figure 3. Median and interquartile range of IOS parameters during exacerbation and recovery are displayed using a box plot. R5: Resistance at 5 Hz, R20: Resistance at 20 Hz, R5−R20: Difference between resistance at 5 Hz and 20 Hz, X5: Reactance at 5 Hz, AX: Reactance area, Fres: Frequency response (n=38).