Received: June 18, 2025
Accepted: July 7, 2025

Acad Med J 2025;5(2):23-31
UDC: 616.21-002.2:616.24-002.2
DOI:
Original article

EVALUATING CHRONIC RHINOSINUSITIS AS A COMORBID DRIVER IN COPD

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Abstract

Introduction: Chronic rhinosinusitis (CRS) is increasingly recognized as a significant comorbidity in patients with chronic obstructive pulmonary disease (COPD), particularly under the framework of the "united airways" model, which emphasizes shared inflammatory mechanisms across the upper and lower respiratory tract.

Aim: To evaluate inflammatory biomarker profiles among COPD patients with and without CRS, and to assess differences across distinct COPD phenotypes—non-exacerbators (NE), frequent exacerbators (E), and asthma-COPD overlap (ACO).

Material and methods: A cross-sectional study was conducted on 36 COPD patients at a university clinic in Skopje, including 21 with CRS and 15 patients without CRS. All participants underwent clinical phenotyping, nasal endoscopy, sinus CT, and serum biomarker analysis (IL-4, IL-5, IL-6, IL-8, CRP, leukocytes). Statistical comparisons were made using Mann–Whitney U and Kruskal–Wallis tests.

Results: CRS was predominantly found in patients with the ACO phenotype (71.4%, $p = 0.0006$). No statistically significant differences were observed in systemic biomarkers (IL-4, IL-5, IL-6, IL-8, CRP, leukocytes) between COPD patients with and without CRS. IL-5 and IL-6 were undetectable. Similarly, inflammatory profiles did not significantly differ among COPD phenotypes.

Conclusion: CRS appears disproportionately represented in the ACO phenotype, likely due to shared type-2 inflammatory pathways. However, conventional systemic biomarkers lack the sensitivity to detect upper airway involvement or differentiate COPD phenotypes. These findings highlight the need for comprehensive airway assessment and more specific biomarkers in future studies to better understand the interplay between CRS and COPD.

Keywords: sinusitis, COPD, inflammatory markers

Introduction

Chronic obstructive pulmonary disease (COPD) and chronic rhinosinusitis (CRS) are connected through what is often described as the "united airways" model. In the early 2000s, researchers began observing that COPD patients frequently report nasal and sinus symptoms, suggesting that inflammation is not confined to the lower airway but is part of a pan-respiratory disease process. Approximately 22-53% of COPD patients also have chronic rhinosinusitis (CRS), though many remain undiagnosed. One study found prevalence of 22.5% (with 82% undiagnosed), while others report rates up to 64% per CT scan regardless of COPD severity[1] Up to 75% of COPD patients report nasal symptoms; over 33% of sinusitis sufferers exhibit

lower airway disease[2]. Even more compelling are CT-based studies: nearly half of subjects show radiological signs consistent with CRS-including mucosal thickening or sinus opacification - resulting in prevalence figures as high as 51%. More broadly, sinonasal symptom prevalence in COPD ranges from 40% to 88% across diverse cohorts[3]. Population-based data from Brazil reinforce the association: 14.7% of adults report rhinosinusitis symptoms, with COPD noted in 8.7% of respondents; smoking emerges as a major driver, significantly correlating with sinonasal symptoms[4]. These findings emphasize the high prevalence of CRS in COPD population and its frequent under-recognition. This association supports subsequent epidemiological and clinical investigations evaluating sinonasal involvement in COPD[1,5].

The "united airways" model suggests that exposures to cigarette smoke, allergens, and irritants trigger inflammatory cascades in both the nasal and bronchial mucosa. Lower airway inflammation may precipitate nasal disease and *vice versa* through mechanisms including the nasal–bronchial reflex and shared inflammatory mediators. Smoking, in particular, impairs mucociliary clearance and contributes to mucosal dysfunction throughout the respiratory tract; one study reported that smokers with COPD exhibit significantly delayed nasal mucociliary transit and elevated biomarkers of oxidative stress in nasal secretions[6,7]. This parallels bronchial dysfunction further supports the conception of COPD as a systemic inflammatory condition extending beyond the lungs. In COPD, persistent neutrophilic inflammation is marked by elevated levels of IL-6, IL-1β, TNF-α, and IL-8 in sputum, bronchoalveolar lavage, and systemic circulation[8,9]. These mediators, along with lipid chemoattractants like leukotriene B_4 and chemokines MCP-1, RANTES, and eotaxin, orchestrate macrophage and neutrophil recruitment, mucus hypersecretion, protease release (such as MMP-9), and airway remodeling. IL-6 serves as a bridge between pulmonary and systemic inflammation, correlating with CRP levels, endothelial dysfunction, comorbidities, and emphysema progression. Th17-driven cytokine IL-17A further amplifies neutrophilic recruitment and steroid resistance in severe phenotypes. Approximately 20-40% of COPD patients exhibit a type 2-high endotype, characterized by elevated blood eosinophils and Th2 cytokines (IL-4, IL-5, IL-13) (3,10). Distinct inflammatory patterns are associated to certain symptom profiles, exacerbation frequency, radiographic features which define distinct clinical subgroups, phenotypes. CRS on the other side, especially associated with nasal polyps, is predominated by type 2 (T2) inflammation. Here, IL-4, IL-5, and IL-13 mediate eosinophil recruitment, IgE production, epithelial barrier disruption, and polyp formation. Chemokines such as eotaxins and MCP-4 further drive eosinophilic infiltration. However, both neutrophilic CRS phenotypes and COPD elevated IL-6, IL-8, TNF-α, IL-17A, TGF-β, and MMPs, reflecting shared inflammatory and remodeling processes[3,10].

Diagnosing CRS in COPD patients poses a challenge because both clinicians and patients tend to concentrate on lower airway manifestations, such as productive cough, wheezing, and dyspnea, while neglecting subtle or non-specific sinus symptoms. Nasal symptoms including nasal obstruction, post-nasal drip, anosmia, and facial discomfort are often misattributed to smoking or the COPD itself. Validated symptom scores, including the SNOT-22 for upper airway burden, the CAT for COPD severity, and the mMRC scale for dyspnea can facilitate early recognition when used in combination. In the presence of concerning symptoms, nasal endoscopy should be performed; CT of the sinuses then enables objective quantification using the Lund–Mackay scoring system, while chest HRCT may reveal comorbid bronchiectasis. Diagnostic nasal endoscopy demonstrates high sensitivity (94%) and acceptable specificity (75%) compared to CT imaging in CRS detection[5,11].

Management of CRS in COPD includes nasal saline irrigation, intranasal corticosteroids, and targeted antibiotics for bacterial CRS. Smoking cessation is critical, as it reduces upper airway inflammation and restores mucociliary clearance to levels approaching those of non-

smokers. Systemic mucolytics such as erdosteine - with antioxidant, mucociliary-enhancing, and anti-adhesive properties - have demonstrated efficacy in reducing COPD exacerbation frequency and duration[6]. For CRS unresponsive to optimal medical therapy, especially when polyps or anatomical blockages are present, functional endoscopic sinus surgery (FESS) offers a logical next step. Precision therapies, including biologic agents such as dupilumab (anti-IL-4/13), hold promise for patients exhibiting type 2 inflammatory phenotypes. Early results in COPD suggest reductions in exacerbation frequency and small gains in FEV_1, though evidence regarding their efficacy in CRS within this population is still emerging. In considering CRS not merely as a comorbidity but a possible driver of COPD progression, it is important to have multidisciplinary comprehensive approach. Targeting CRS fits within this broader strategy by reducing upper airway inflammatory burden[8,11].

Aim

This study aimed to determine the inflammatory biomarker profiles associated with each COPD phenotype, identify differences between patients with and without concurrent chronic rhinosinusitis (CRS), and assess potential significant variations among different COPD phenotypes.

Material and methods

We conducted a cross-sectional comparative study comprising 36 patients diagnosed with chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines at the University Clinic of Pulmonology and Allergy, Faculty of Medicine, Skopje. All participants were over 18 years of age and provided informed consent. Each patient underwent a comprehensive evaluation, including detailed medical history, spirometry following ERS guidelines, nasal endoscopy, sinus CT scans using standard protocol, and venous blood sampling to assess levels of interleukins (IL-4, IL-5, IL-6, IL-8 with Luminex technology), C-reactive protein (CRP), and total leukocyte count. Participants were categorized into three groups of clinical COPD phenotypes:

1. Non-exacerbator (NE): Patients with at most one moderate exacerbation and no severe exacerbations in the past 12 months.
2. Frequent exacerbator (E): Patients with two or more moderate exacerbations or at least one severe exacerbation requiring hospitalization in the past year.
3. Asthma-COPD Overlap (ACO): Patients exhibiting clinical features of both asthma and COPD, regardless of exacerbation frequency.

Results

In our study, a total of 36 participants were enrolled: COPD-CRS group of 21 patient with chronic obstructive pulmonary disease (COPD) and chronic rhinosinusitis (CRS), and a control group of 15 patients with COPD without CRS. All patients were active or ex-smokers. Among the COPD-CRS group, 5 were classified as non-exacerbators (NE), 1 as a frequent exacerbator (E), and 15 as having the asthma-COPD overlap (ACO) phenotype. This distribution indicated a significant predominance of CRS in the ACO phenotype (Figure 1).

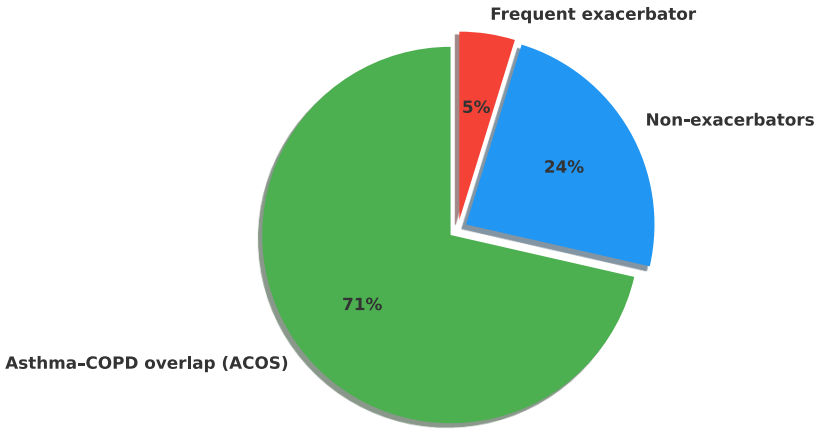

Fig. 1. Patient distribution across COPD phenotypes

Inflammatory parameters were determined for the two groups. Descriptive analysis of the inflammatory parameters values is shown in Table 1.

Table 1. Inflammatory parameters in COPD with and without CRS

Inflammatory parameter	COPD - CRS (n = 21)	COPD (n = 15)
IL-5, IL-6	0 (undetectable)	0 (undetectable)
IL-8	26.45±21.76 pg/mL Median 20.40 [24.98]	29.88±21.48 pg/mL Median 24.42 [10.65]
IL-4	4.98±12.27 pg/mL Median 0 [0]	2.31±8.96 pg/mL Median 0 [0]
Leukocytes (Le)(×10⁹/L)	8.02±1.59 Median 7.50 [2.50]	8.58±1.83 Median 8.50 [2.80]
CRP (mg/L)	6.09±4.36 Median 5.00 [2.10]	6.98±4.66 Median 6.00 [8.00]

Both IL-5 and IL-6 levels were below the assay's lower limit of detection, and could not make distinction between the groups. Il- 8 showed a wide distribution in both cohorts (Figure 1). IL-4 levels were zero; the mean levels were inflated by a few outliers. White blood cell counts were slightly higher in COPD-only patients, but distributions showed extensive overlap (Figure 2). Very similar systemic inflammation in both groups was shown by CRP levels, with a few high outliers (Figure 3).

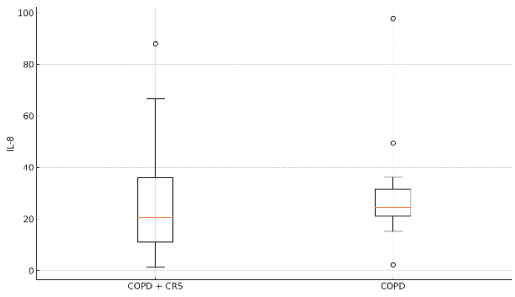

Fig. 1. IL-8 distribution

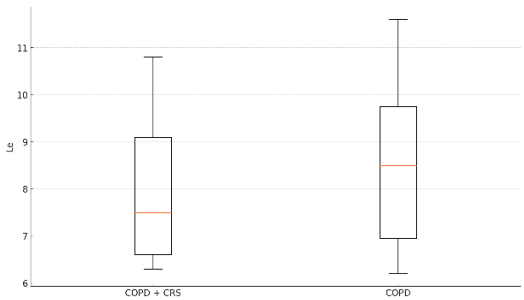

Fig. 2. White blood cell distribution

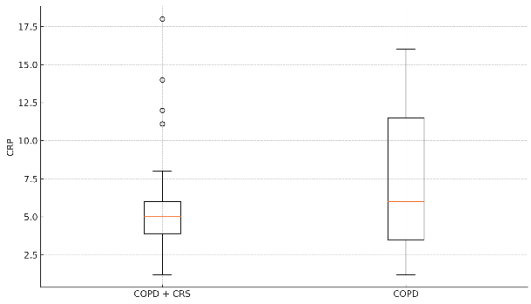

Figure 3. CRP levels

The comparisons between the groups of COPD with and without CRS using the Mann–Whitney U test did not show a biomarker that clearly distinguished the groups. All p-values were above the conventional 0.05 threshold and the rank-biserial effect sizes were in the small (< 0.3) or trivial (< 0.1) range (Table 2).

Table 2. Group comparison of inflammatory parameters between COPD with and without CRS

Inflammatory parameter	p-value	Effect size
IL-5, IL-6	—	—
IL-8	0.3121	r=0.203 (small)
IL-4	0.3235	r=-0.121 (small)
Leukocytes	0.4211	r=0.162 (small)
CRP	0.6294	r=0.098 (trivial)

IL-5 and IL-6 were undetectable in both cohorts. IL-8 showed a weak, non-significant trend. COPD patients had slightly higher IL-8 median levels (24.4 pg/mL *vs* 20.4), but the spread was enormous and distributions overlapped almost completely, which was reflected in a small effect size (r≈0.20) and non-significant p-value (0.31). IL-4 was essentially zero in most patients. A few outliers in the CRS group elevated the mean; the median levels were zero in both groups, again indicating poor discriminatory value. Systemic inflammation (CRP, leukocytes) was comparable. Median CRP levels ranged from 5 to 6 mg/L in both cohorts, and overlapping leukocyte counts suggested that co-existing CRS did not add an obvious systemic inflammatory burden to COPD patients in this sample.

The statistical power of our sample is limited. With 21 *vs.* 15 patients, the study is powered only to detect large effects (r≥0.5 or Cohen's d≥0.8). Small differences might have gone undetected; a larger cohort would be required to confirm the null findings.

Table 3. Summarized Descriptive Statistics by Phenotype

Inflammatory parameter	ACOS (n=15)	Non-Exacerbators (n=5)	Frequent Exacerbators (n=1)
IL-6	0 (undetectable)	0 (undetectable)	0 (undetectable)
IL-8	26.73±23.62 Median 20.4 [25.0]	33.88±20.45 Median 30.2 [17.4]	15.15
IL-4	5.13±13.38 Median 0 [0]	5.88±13.14 Median 0 [0]	0
IL-5	0 (undetectable)	0 (undetectable)	0
Leukocytes	7.93±1.64 Median 7.5 [2.5]	7.94±1.85 Median 7.5 [2.6]	10.8
CRP	5.96±4.60 Median 5.0 [2.1]	4.36±2.29 Median 4.0 [3.4]	8.0

Further on, we analyzed and compared the inflammatory parameters among the three COPD phenotypes. The summarized descriptive statistics by phenotype is shown in Tables 3 and 4.

Table 4. Kruskal–Wallis Test Results

Marker	H-statistic	*p*-value	Interpretation
IL-6	—	—	No variance (all values zero)
IL-8	1.025	0.5990	Not significant
IL-4	1.297	0.5230	Not significant
IL-5	—	—	No variance (all values zero)
Leukocytes	2.574	0.2761	Not significant
CRP	3.247	0.1970	Not significant

All p-values were >0.05, indicating that no statistically significant differences between the phenotypes for any inflammatory marker were found.

Discussion

This study explored the inflammatory profile of patients with coexisting Chronic Obstructive Pulmonary Disease (COPD) and Chronic Rhinosinusitis (CRS), with a particular focus on inflammatory biomarkers (IL-6, IL-8, IL-4, IL-5, CRP, and leukocyte count). The secondary aim was to investigate whether different clinical phenotypes of COPD within the CRS cohort, namely asthma-COPD overlap (ACOS), non-exacerbators, and frequent exacerbators, exhibited distinct inflammatory patterns.

There was a significant predominance of chronic rhinosinusitis (CRS) among patients with the asthma-COPD overlap (ACO) phenotype. This aligns with emerging evidence suggesting that ACO represents a distinct disease entity marked by overlapping inflammatory pathways, including heightened type-2 immunity. Population-based meta-analyses report ACO in approximately 30% of COPD patients, considerably higher than the 2% prevalence in the general population[12]. ACO patients typically exhibit more severe symptoms, greater exacerbation frequency, and increased comorbidity than those with asthma or COPD alone[13]. Although CRS has not been consistently quantified in ACO populations, its association with asthma and eosinophilic inflammation suggests a higher burden in this subgroup. Our finding of CRS significant predominance in ACO patients thus reflects a broader pattern: ACO phenotypes, driven by T2 inflammation and airway hyperresponsiveness, are predisposed to sinonasal comorbidity. Recognizing CRS within this subgroup is essential, as it may exacerbate lower-airway inflammation, worsen COPD outcomes, and offer novel therapeutic targets such as type-2 biologics.

The inability to measure IL-5 and IL-6 in both groups aligns with previous studies showing that many COPD patients, especially those with milder disease or in stable phases, have very low or undetectable circulating levels of these cytokines[14]. In a large population-based COPD cohort, median IL-6 was as low as 1.9 pg/mL, with values bordering assay sensitivity. Thus, the lack of signal in this study likely reflects both disease stability and assay constraints, rather than true biological absence. IL-8 in our results showed substantial variability in COPD cohorts. Several studies demonstrated broad distributions of IL-8 across disease severities, with median values around 2–10 pg/mL and considerable overlap between groups. This variability makes IL-8 a poor discriminator of comorbid CRS within COPD[15]. IL-4 is primarily elevated in T2-driven asthma phenotypes and CRS with nasal polyps, but remains negligible in most COPD patients[16]. Thus, the near-zero majority with occasional high outliers in IL-4 is consistent with literature and reflects phenotype heterogeneity. White blood cell counts are known to increase modestly in COPD, particularly during exacerbations, but can overlap significantly between stable and comorbid groups. Our observation of slight

elevation without clear separation is therefore expected. CRP in stable COPD often shows only mild elevation, with large inter-individual variance[17]. Although higher CRP may correlate with exacerbation risk, its overlap between COPD patients with and without CRS is widely reported and reflects non-specific acute-phase behavior[18,19]. Taken together, our data demonstrate that routine systemic biomarkers - IL-4, IL-5, IL-6, IL-8, Le and CRP lack sufficient specificity or sensitivity to distinguish CRS comorbidity within COPD. This aligns with the literature, which shows that while these markers reflect general inflammatory activity, they fail to discriminate upper airway involvement. Future studies should incorporate more targeted biomarkers (e.g., eosinophil-derived proteins, local nasal cytokine levels) or advanced phenotyping (biomarker panels, cluster analysis) to better detect CRS in COPD populations.

No statistically significant differences were observed between the COPD phenotypes for any of the analyzed inflammatory markers. Meta-analyses and cohort studies have consistently shown that stable COPD is associated with mildly elevated systemic markers, such as IL-6, IL-8, CRP, and leukocyte count compared to healthy controls, but these elevations do not clearly discriminate between clinical phenotypes or disease severity[20]. Large cohort studies like ECLIPSE identify a subgroup with persistently elevated inflammation (based on CRP, IL-6, IL-8, fibrinogen, and leukocyte levels) correlating with worse outcomes. However, this “inflamed phenotype” does not align specifically with traditional clinical phenotypes such as ACO, exacerbator, or non-exacerbator[21]. Research confirms that systemic biomarkers - including CRP, WBC, IL-6, and IL-8 - fail to differentiate COPD phenotypes defined by exacerbation history, emphysema/chronic bronchitis dominance, or ACO status[22].

These findings suggest that the presence of CRS in patients with COPD does not appear to exacerbate systemic inflammation, at least as measured by the selected cytokines and acute-phase reactants. The COPD phenotype, despite its clinical relevance for treatment and prognosis, does not strongly stratify inflammatory marker levels within the CRS group, possibly due to shared mechanisms or insufficient systemic spill-over. The complete lack of detectable IL-6 and IL-5 supports previous reports that local nasal and bronchial inflammation may not always translate into measurable systemic cytokine elevations, particularly during stable clinical phases.

The primary limitation of our study is the sample size, which limits statistical power for subgroup comparisons. The cross-sectional design precludes assessment of inflammatory variation over time or during exacerbations. Only serum markers were used; nasal lavage or induced sputum could offer more localized insight.

Conclusion

In summary, chronic rhinosinusitis is a frequently overlooked but clinically significant comorbidity in COPD, affecting nearly half of patients, particularly those with severe disease or active smokers. The shared inflammatory pathways and overlapping symptom profiles demand a unified airway approach. Our finding that CRS predominates within the ACO COPD phenotype is both statistically and pathophysiologically justified. ACO’s type-2-driven inflammation creates fertile ground for sinonasal involvement. This emphasizes the critical need for integrated assessment of upper airway disease in ACO presentations and supports a unified airway approach to management. Selected inflammatory markers reflect general inflammatory activity, but they fail to discriminate upper airway involvement.

The absence of statistically significant biomarker differences among COPD phenotypes in our study is consistent with broader evidence: while these markers indicate systemic inflammation in COPD, they lack specificity and sensitivity to distinguish clinical phenotypes. This suggests that phenotype-specific inflammation is likely localized or subtle. Future research should focus on more nuanced biomarkers, including sputum or tissue cytokines, cell-

specific signatures, or composite panels, to uncover phenotype-specific inflammatory pathways.

Conflict of interest statement. None declared.

References

1. Arndal E, Sørensen AL, Lapperre TS, Said N, Trampedach C, Aanæs K, Alanin MC, Christensen KB, Backer V, von Buchwald C. Chronic rhinosinusitis in COPD: A prevalent but unrecognized comorbidity impacting health related quality of life. *Respir Med* 2020; 171: 106092. doi: 10.1016/j.rmed.2020.106092.
2. Kim JS, Rubin BK. Nasal and sinus inflammation in chronic obstructive pulmonary disease. COPD. 2007; 4(2): 163-166. doi: 10.1080/15412550701341228.
3. Øie MR, Helvik AS, Sue-Chu M, Steinsvåg SK, Thorstensen WM. Sinonasal Symptoms in COPD: Burden and Associations with Clinical Markers of Disease. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 2137-2147. doi: 10.2147/COPD.S372991. Erratum in: Int J Chron Obstruct Pulmon Dis. 2022 Oct 28;17:2789-2790. doi: 10.2147/COPD.S392892.
4. Caminha GP, Pizzichini E, Lubianca Neto JF, Hopkins C, Moreira JDS, Pizzichini MMM. Rhinosinusitis symptoms, smoking and COPD: Prevalence and associations. *Clin Otolaryngol* 2018; 43(6): 1560-1565. doi: 10.1111/coa.13215.
5. Deosthale NV, Khadakkar SP, Harkare VV, Dhoke PR, Dhote KS, Soni AJ, *et al*. Diagnostic Accuracy of Nasal Endoscopy as Compared to Computed Tomography in Chronic Rhinosinusitis. *Indian J Otolaryngol Head Neck Surg* 2017; 69(4):494-499. doi: 10.1007/s12070-017-1232-0.
6. Yii ACA, Tay TR, Choo XN, Koh MSY, Tee AKH, Wang DY. Precision medicine in united airways disease: A "treatable traits" approach. *Allergy* 2018; 73(10): 1964-1978. doi: 10.1111/all.13496.
7. Håkansson K, von Buchwald C, Thomsen SF, Thyssen JP, Backer V, Linneberg A. Nonallergic rhinitis and its association with smoking and lower airway disease: A general population study. *Am J Rhinol Allergy* 2011; 25(1): 25-29. doi: 10.2500/ajra.2011.25.3556.
8. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. *Am J Respir Crit Care Med* 2019; 199(10): 1195-1204. doi: 10.1164/rccm.201810-1860SO.
9. Pantazopoulos I, Magounaki K, Kotsiou O, Rouka E, Perlikos F, Kakavas S, *et al*. Incorporating Biomarkers in COPD Management: The Research Keeps Going. *J Pers Med* 2022; 12(3): 379. doi: 10.3390/jpm12030379.
10. Gonçalves I, Guimarães MJ, van Zeller M, Menezes F, Moita J, Simão P. Clinical and molecular markers in COPD. *Pulmonology* 2018; 24(4): 250-259. doi: 10.1016/j.pulmoe.2018.02.005.
11. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, *et al*. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012; 50(1): 1-12. doi: 10.4193/Rhino12.000.
12. Hosseini M, Almasi-Hashiani A, Sepidarkish M, Maroufizadeh S. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respir Res* 2019; 20(1): 229. doi: 10.1186/s12931-019-1198-4.
13. Kobayashi S, Hanagama M, Ishida M, Ono M, Sato H, Yamanda S, *et al*. Clinical Characteristics and Outcomes of Patients with Asthma-COPD Overlap in Japanese Patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 2923-2929. doi: 10.2147/COPD.S276314.

14. Su B, Liu T, Fan H, Chen F, Ding H, Wu Z, *et al*. Inflammatory Markers and the Risk of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11(4): e0150586. doi: 10.1371/journal.pone.0150586.
15. Pease JE, Sabroe I. The role of interleukin-8 and its receptors in inflammatory lung disease: implications for therapy. *Am J Respir Med* 2002; 1(1): 19-25. doi: 10.1007/BF03257159.
16. King PT. Inflammation in chronic obstructive pulmonary disease and its role in cardiovascular disease and lung cancer. *Clin Transl Med* 2015; 4(1): 68. doi: 10.1186/s40169-015-0068-z.
17. Wouters EF, Groenewegen KH, Dentener MA, Vernooy JH. Systemic inflammation in chronic obstructive pulmonary disease: the role of exacerbations. *Proc Am Thorac Soc* 2007; 4(8): 626-634. doi: 10.1513/pats.200706-071TH.
18. Yıldırım YS, Apuhan T, Koçoğlu E, Simşek T, Kazaz H. High sensitivity C-reactive protein levels in chronic rhinosinusitis and allergic rhinitis. *Kulak Burun Bogaz Ihtis Derg* 2011; 21(5): 266-269. doi: 10.5606/kbbihtisas.2011.039.
19. Aksu F, Capan N, Aksu K, Ofluoğlu R, Canbakan S, Yavuz B, Akin KO. C-reactive protein levels are raised in stable Chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. *J Thorac Dis* 2013; 5(4): 414-421. doi: 10.3978/j.issn.2072-1439.2013.06.27.
20. Wei J, Xiong XF, Lin YH, Zheng BX, Cheng DY. Association between serum interleukin-6 concentrations and chronic obstructive pulmonary disease: a systematic review and meta-analysis. *PeerJ* 2015; 3: e1199. doi: 10.7717/peerj.1199.
21. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, *et al*. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7(5): e37483. doi: 10.1371/journal.pone.0037483.
22. Sonar M, Jayadeva BT, Shashibhushan BL. Comparative Study of Systemic Inflammatory Markers in Clinical Phenotypes of Chronic Obstructive Pulmonary Disease. *Tanaffos* 2023; 22(2): 215-220. PMID: 38628879.