JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Review Article DOI: https://doi.org/10.23950/jcmk/14640

Eosinophilic Inflammation in COPD: Mechanisms, Diagnostic Markers, Clinical Features and Therapy Guidance

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Received: 2024-02-25.
Accepted: 2024-05-19.

J Clin Med Kaz 2024; 21(3):4-10

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Abstract

Chronic obstructive pulmonary disease (COPD) is one of the main causes of morbidity and mortality worldwide. Eosinophilia, which may have a significant role in the inflammation process and obstruction of airways, is present in about one third patients suffering from COPD. The significance of eosinophil counts in COPD is currently debated, but they can potentially serve as biomarkers for treatment selection. Blood eosinophil counts can assist in determining the patients who can benefit from inhaled corticosteroid therapy to prevent or eliminate exacerbations.

The aim of this review is to demonstrate the significance of eosinophilic inflammation COPD and the use of eosinophilic inflammation biomarkers to guide therapy decisions.

To reach this goal, a search of relevant literature on the subject was conducted. Articles were searched in electronic sources: PubMed and Google Scholar. The keywords "COPD and eosinophilia", "COPD exacerbations and eosinophilia", "inhaled corticosteroids, COPD and eosinophilia" were used. One hundred and twenty sources were found, of which 66 were selected.

Results of the review showed high frequency of eosinophilic phenotype detection in COPD. Blood eosinophilia becomes a potential universal marker of eosinophilic COPD. Blood eosinophils level can predict response to inhaled corticosteroids treatment patients with COPD, but increases the likelihood of pneumonia. Overall, the role of eosinophilia in COPD has not been obtained to date, which suggests it needs further study.

Keywords: chronic obstructive pulmonary disease; eosinophilia; inflammation; biomarkers; treatment outcome; corticosteroids; exacerbations; pneumonia; phenotype; personalized medicine.

Introduction

Chronic obstructive pulmonary disease (COPD) has a severe negative socio-economic impact on the healthcare system, causing significant mortality and disability worldwide [1-3]. Data shows that COPD causes 2.8 million deaths annually, which corresponds to about 5% of all deaths in the world [2]. Studies on the epidemiology of COPD in Kazakhstan are not numerous but indicate a high prevalence [4, 5]. According to the results of the Chronic Obstructive Respiratory disease study, carried out between 2013-2015 in Commonwealth of Independent States countries, the prevalence of COPD in Kazakhstan was found to be 114.1 per 1000 population [4]. In the near future, an increase in morbidity and mortality from COPD is expected due to the associated prevalence of tobacco smoking, environmental pollution, and increasing age of the population [6-9].

Chronic exposure to toxic particulates and gases leads to the development of COPD. Due to the influence of these factors, persistent inflammation with a complex

heterogeneous mechanism develops [10]. For a long time, the main cell responsible for the airway inflammation in COPD was considered to be the neutrophil, whereas eosinophilic airway inflammation was seen as typical for bronchial asthma [11-13]. However, there is increasing evidence of high eosinophil activity in a number of patients with COPD [14].

This review aims to describe the role of eosinophils in COPD, how they are related to clinical progression and prognosis, and how they can affect the choice of therapy.

A literature search was conducted on the topic of eosinophilia in COPD. Articles were searched in electronic sources: PubMed and Google Scholar. The keywords "COPD and eosinophilia", "COPD exacerbations and eosinophilia", "inhaled corticosteroids, COPD and eosinophilia" were used. One hundred and twenty sources were found, of which 66 were selected.

Prevalence of eosinophilic COPD

According to the results of the 3-year ECLIPSE study of COPD patients, which used a threshold level of 2% for blood eosinophilia: 37.4% of participants had persistent peripheral eosinophilia (>2%), 49% had variable eosinophil levels, and only 13.6% of patients had no peripheral eosinophilia at any visit [15]. Cross-sectional study by Bedolla-Barajas et al. demonstrated that out of 81 patients with COPD, 34 (42%) had a relative eosinophil concentration ≥2%; 21 (25.9%) ≥3%; 14 patients (17.3%) had ≥4%; and 10 patients (12.3%) had ≥5% [16]. A retrospective cohort study in China (2012-2015) by Yang et al., which selected 375 COPD patients, stratified them based on the blood eosinophil count into 3 groups, showed that: 125 patients had less than 100 eosinophils/μL, 195 patients had between 100-300 eosinophils/μL, and 55 patients had eosinophil count greater than 300 eosinophils/μL in the blood. The prevalence of eosinophilic COPD in that cohort demonstrated to be 66.7%, if the cut-off of 100 eosinophils/μL is used, and 14.7% if cut-off of 300 eosinophils/μL is used [17]. To date, COPD with eosinophilic inflammation is a distinct disease phenotype with its own characteristic clinical features [18, 19]. It has been shown that 25-40% of cases of COPD can present with eosinophilia [15]. Additionally eosinophilic inflammation was shown to be present in 28% of acute exacerbations of the disease [20].

Mechanism and markers of eosinophilic inflammation in COPD

The mechanism of eosinophilia development in COPD currently is not fully understood. However, the previous studies have indicated that eosinophilic inflammation in COPD patients correlates with an increase of cytokine Interleukin 5 (IL-5) in the respiratory tract [21]. This cytokine is produced by Th2 cells, ILC2 cells and it promotes differentiation, migration, activation, and effector functions of eosinophils [22, 23]. Another cytokine that promotes proliferation of hematopoietic cells into mature eosinophils is granulocyte-macrophage colony-stimulating factor [22]. As shown in Figure 1, the proinflammatory effect of eosinophils occurs through various mechanisms. The major basic protein of eosinophils disrupts epithelial permeability, promoting the penetration of antigens into the respiratory tract, eosinophil peroxidase causes tissue damage via oxidative stress, eosinophil cationic protein leads to the apoptosis of respiratory epithelium [24]. Cytokines and chemokines such as IL5, IL10, CCL5 also lead to development and persistence of eosinophilic inflammation. Sustained inflammation leads to oedema, basal membrane thickening, airway remodeling, and mucus hypersecretion [25, 26].

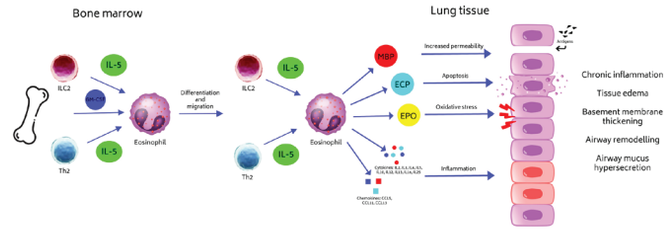

Figure 1 - Pathophysiology of eosinophilic inflammation in COPD: IL-5: interleukin 5, ILC2: type 2 innate lymphoid cell, Th2: T helper 2 cell, GM-CSF: granulocyte-macrophage colony-stimulating factor, MBP: major basic protein, ECP: eosinophil cationic protein, EPO: eosinophil peroxidase, IL2-25: interleukins 2-25, CCL5, 11, 13: chemokine ligand 5, 11, 13

There are several methods to estimate the severity of eosinophilic inflammation. The most common approaches are based on the estimation of eosinophil counts in various samples of biological material. For this purpose, biopsy material may be examined, sputum specimens obtained by conventional methods may be analyzed and induced sputum and bronchoalveolar lavage fluid may be analyzed.

A normal eosinophil count in induced sputum is <3% [27]. Elevation of eosinophils over 3% is a criterion for eosinophilic COPD and happens in 28% of all COPD exacerbations [20], as well as in 34-38% of COPD patients during the stable period [28]. It should be noted that cytological analysis of induced sputum is methodologically difficult and time consuming for most clinical laboratories and in many cases is not readily available in real clinical practice. Obtaining sufficient quantities of spontaneous sputum is technically challenging, as confirmed in the results of the SPIROMICS study [29]. Kolsum et al. revealed that blood eosinophilia is a marker of sputum eosinophilia. Patients with peripheral blood eosinophilia had higher levels of eosinophils in sputum: median percentage count 7.0%, compared to 2.5% in a group with no eosinophilia, $p = 0.002$, median absolute sputum eosinophil count 0.4 vs. 0.1, $p < 0.01$ [30]. Negewo et al. also demonstrated the relation of sputum eosinophilia to peripheral blood eosinophilia. Patients with sputum eosinophilia had a blood eosinophil count of 300 cells/μL, while the patients with normal sputum eosinophil levels had blood eosinophil count 150 cells/μL, $p<0.0001$) [31]. In a study by Singh et al., both percentage and absolute blood eosinophils positively correlated with the presence of eosinophils in sputum ($r=0.54$, $p<0.0001$) [32].

Recently, the blood eosinophilia threshold of 300 cells/μL is increasingly used as the most accurate marker of eosinophilic inflammation and with a subsequent positive response to inhaled corticosteroid (ICS) therapy [33, 34]. One of the limitations in using eosinophilia as a biomarker is its variability from day to day and throughout the day. According to Oshagbemi et al., in COPD patients, stable eosinophil counts (counts that are persistently above or below the threshold of 340 cells/μL) at 6 months of follow-up were observed in 85% of measurements, 62% at 2 years, then decreased afterwards [35]. Analysis of 2 prospective observational studies CHAIN and BODE conducted in Spain from 2016-2018 confirms the significant variability of eosinophilia in COPD patients over time: 40.5% of patients had an intermittently variable eosinophilia, defined as variation in eosinophil counts between ≥300 or <300 cells/μL in 3 assessments. 43.8% had a constantly normal eosinophil count, while only 15.7% had persistent eosinophilia [36].

Nitric oxide in exhaled air (FeNO) is a biomarker that has been shown to help distinguish eosinophilic from non-eosinophilic airway inflammation [37]. FeNO is positively correlated with eosinophil counts in induced sputum during COPD exacerbation [38]. Research by Tang et al. demonstrated a connection between FeNO and peripheral blood eosinophil count: blood eosinophilia positively correlated with FeNO (r=0.383, p=0.004) [39].

The above allows us to consider blood eosinophilia to be a surrogate for presence of eosinophilic inflammation in the airway. It should be noted that blood analysis, unlike the study of induced sputum, is widely available, easy to perform and can be performed in all patients, so the blood eosinophil count deserves the closest attention for the phenotypic characterization of inflammation in COPD.

Clinical features in eosinophilic COPD

Several studies have demonstrated that higher blood levels of eosinophils correlated with increased risk of re-hospitalization, prolonged hospitalizations, and worse lung function [40, 41]. Longitudinal prospective study ECLIPSE found that, COPD patients with blood eosinophilia ≥2% were characterized by higher values of the forced expiratory volume in 1 second (FEV1), lower body fat, less severe dyspnea measured by the modified Medical Research Council (mMRC) scale, higher scores on St. George's Respiratory Questionnaire which assessed life quality [15]. According to the study by Turato et al., patients were categorized into three distinct groups: those with a persistent elevatedeosinophil count (≥150 cells/μL), low eosinophil count (<150 cells/μL), and variable (fluctuating over/ below 150 cells/μL) eosinophil count. The study showed no notable distinctions among the groups regarding smoking history, results of spirometry, COPD severity, frequency of exacerbations, mMRC scale score, and exercise tolerance (according to the 6-minute walk test) [42]. As shown in the study by Chou et al., sputum eosinophil levels correlated weakly with the degree of reversibility of FEV1 (r=0.162, p=008.1) [43]. The differences between non-eosinophilic and eosinophilic COPD in terms of FEV1 and mMRC were found to be not-significant in a study of 7225 patients by Vedel-Krogh et al. [19].

At this point, the relation between sputum or blood eosinophilia, with severity of pulmonary emphysema in COPD patients is not clear. One study conducted in Greece, had shown that presence of emphysema was associated with significantly lower blood eosinophils: median absolute count 34.6 cells/μL (Interquartile range (IQR) 0-63) in emphysema group compared to 169.0 cells/μL (IQR 110-260) in non-emphysema group, p<0.001. Same was true for percent eosinophil count: median 0.6% (IQR 0-1%) vs. 3.0% (IQR 2-4%), p < 0.001 [44]. Same findings were confirmed in a study conducted in Korea by Oh et al. in 2018 [45]. Another study by Hastie et al. showed that increased eosinophils in sputum were related to higher exacerbation risk and more prominent emphysema, whilst no such relationship was observed for blood eosinophil levels [29].

Based on the above, convincing relation between clinical and functional parameters and eosinophilia in COPD has not been shown to date, which suggests it needs further study.

Exacerbations and prognosis in eosinophilic COPD

COPD exacerbations are considered extremely important in clinical practice as they are related to the disease prognosis, so risk of COPD exacerbations and their relationship with eosinophilia are actively investigated [46-48]. Cheng et al. observed that severe exacerbations were more common with baseline blood eosinophil levels ≥ 3%, compared to eosinophil levels <3% (27.1% vs. 7.4%; p<0.01) [49].

Vedel-Krogh et al. showed in 203 COPD patients that an increase in eosinophil count >340 cells/μL and a history of single exacerbation per year were linked to a 3.21-fold higher risk of severe exacerbations, additionally an increase in blood eosinophil count >2% corresponded with a 1.85 times higher risk of severe exacerbations [19]. Retrospective cohort study, which utilized the UK Clinical practice Research Datalink (CPRD) and US Optum Clinformatics Data Mart (Optum) databases, showed that among COPD patients with several (≥2) exacerbations per year, majority of patients: 76.8% in the CPRD database and 76.5% in the Optum database, had peripheral blood eosinophilia ≥300 cells/μL during one year of follow-up, while a significant minority: 17.0% in CPRD database, and 13.3% in Optum database had peripheral blood eosinophilia ≥400 cells/μL [50]. Yun and colleagues reported that higher blood eosinophil levels were linked to an increased risk of COPD exacerbations, with an eosinophil threshold of ≥300 cells/μL showing an adjusted incidence rate ratio for exacerbations of 1.32 (95% confidence interval (CI) 1.10-1.63) [51].

In a retrospective study by Müllerová et al., a subgroup of COPD patients receiving triple therapy with blood eosinophilia >150 cells/μL and a history of frequent exacerbations (n=2512) was analyzed. The RR of moderate and severe COPD exacerbations in this group was 2.32 (95% CI 2.22-2.43), the RR of non-COPD hospitalizations was 1.31 (95% CI 1.18-1.46) and the RR of all-cause mortality was 1.26 (95% CI 1.16-1.37). The researchers concluded that eosinophilic COPD is more resistant to triple therapy leading to a more severe disease and exacerbations [46]. Khamitov et al. in a retrospective study of 424 medical histories of hospitalized patients with COPD exacerbations over 4 calendar years (2015-2018), found that extremely severe obstructions were associated with higher eosinophil counts [52].

On the contrary, Acet-Öztürk and colleagues revealed that COPD patients with elevated eosinophil counts (≥2%) had fewer symptoms and reported higher quality of life in comparison to those with non-eosinophilic inflammation. Non-eosinophilic inflammation was more frequently linked with use of supplemental long-term oxygen therapy in comparison to eosinophilic inflammation (36.1% vs. 14.8%, p = 0.01) [53]. In a UK study where eosinophilia was defined as ≥200 cells/μL the length of hospitalization was shorter in the eosinophilic group compared to patients with non-eosinophilic exacerbations (5.0 days [range, 1-19 days] vs. 6.5 days [range, 1-33 days]; P = 0.015) [54].

Zysman et al. showed that at all cut-off values for eosinophilia (2; 3 or 4%) no significant differences in exacerbation frequency and 3-year survival, between patients with eosinophilic and non-eosinophilic COPD, were found [55]. Additionally retrospective study carried out in Tunisia, the aim of which was to show the relationship between the degree of eosinophilia and various parameters of severity of severe exacerbation of COPD, where the two groups were defined with eosinophils ≥ 200 cells/μL (103 cases, 20.4%), eosinophils < 200 cells/μL (403 patients: 79.6%), there was no notable variance in the course of severe exacerbation of COPD [56].

In the study by Turato et al., 867 patients with COPD died from various causes during the 5-year follow-up. Kaplan-Meier analysis revealed that patients with persistent blood eosinophilia had a higher survival rate (p<0.01) [42]. Another study had corresponding findings; with the median follow-up of 6 years, lower mortality rate was found in patients with COPD and blood eosinophilia ≥ 300 cells/μL (relative risk (RR) 0.29; 95% CI 0.09-0.97, p=0.045) [33].

Oh et al. confirm this in their study where patients with COPD were categorized into three groups based on their blood eosinophil count: high (≥5%), medium (2%-5%), and low (<2%). They found that participants in the group with high counts had longer survival time compared to those with medium or low counts (high = 9.52±0.23 years, medium = 8.47±1.94 years, low = 7.42±0.27 years; p<0.05) [45].

In summary, data on eosinophilic inflammation contributing to a negative prognostic outcome in COPD is still conflicting.

Efficacy of glucocorticosteroid therapy in eosinophilic COPD

Eosinophilic airway inflammation and blood eosinophil levels > 2% are correlated with the responsiveness of COPD patients to systemic glucocorticosteroid therapy for COPD exacerbations [57, 58]. In a study led by Ramarikshan et al., individuals who were current or former smokers with COPD diagnosis were allocated into two groups. The first group received oral prednisolone for 14 days once per day if their blood eosinophil level was higher than 2% or placebo if their eosinophil count was lower than 2%. The second group received standard care therapy irrespective of the blood eosinophil results. Both groups received antibiotic therapy. Practical implication of this non-inferiority trial showed that prednisolone therapy provided to patients according to their blood eosinophil count during the acute phase of COPD was non-inferior to the standardized care tactics and can be provided to patient to reduce potential risks related to the glucocorticoid therapy side effects [59]. There was a meta-analysis conducted by Bafadhel et al. of six clinical trials (300 cases of COPD exacerbations included), according to which similar findings were observed. In patients who did not receive prednisolone during the exacerbation and had blood eosinophil levels < 2%, therapy was ineffective in 20% of cases, with blood eosinophil levels ≥ 2% - in 66% of cases. In patients who received prednisolone and had blood eosinophil levels < 2%, therapy was ineffective in 26% of cases, and when the level was ≥ 2%, therapy was ineffective in 11% of cases [60].

In the prospective randomized study by Cheng et al., patients with COPD used a high dose of fluticasone 1 mcg/day or a medium dose of fluticasone 0.5 mcg/day combined with salmeterol (500 mcg/day). In this research, participants were separated into two groups based on their eosinophil counts: a group with high eosinophil levels (≥3%) and a group with low eosinophil levels (<3%). The group with high eosinophil counts who received higher doses of ICS showed a significant improvement in quality of life (determined by COPD assessment test) compared to the group with low eosinophil counts who received a medium dose of ICS (P=0.02). The incidence of exacerbations was decreased in patients in the first group compared to the second group (13.5% vs. 28.7%, P<0.01) [49]. A retrospective analysis of two 12-month randomized clinical trials comparing vilanterol and fluticasone furoate/vilanterol in COPD patients (n=3177) revealed that ICS reduced exacerbations in individuals with blood eosinophils ≥2%. Participants with eosinophil counts <2 % experienced a 10% reduction in exacerbations, while those with eosinophilia levels of 2-4%, 4-6%, and ≥6% saw reductions of 24%, 32%, and 42%, respectively [61].

Currently, ICS therapy is recommended for patients with blood eosinophil counts exceeding 300 cells/μL, as it is illustrated in Figure 2.

A study conducted over three years in Copenhagen, involving both healthy people and those with COPD, examined the link between blood eosinophils and the risk of COPD exacerbations. From a total population of 81,668 people, 7,225

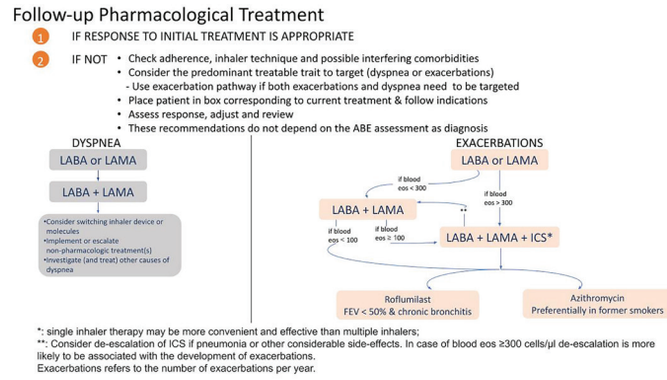

Figure 2 - Global Initiative for Chronic Obstructive Lung Disease 2023 recommendations for use of ICS in COPD [8]

patients with COPD were selected after spirometric respiratory function measurement. Among them, a subgroup of 203 patients who had experienced one or more exacerbations requiring systemic glucocorticoids or hospitalization in the year prior to the study was identified. In particular, the study found that the risk of severe exacerbations was higher in COPD patients with eosinophil counts exceeding 340 cells/μL in the blood, with adjusted incidence rate ratios of 1.76 (95% CI 1.56–1.99), which aligns with aforementioned blood eosinophil count of 300 cells/μL that requires ICS therapy as it is demonstrated in Figure 2 . Using a blood eosinophil count of 2% as a cut-off value, the risk of severe exacerbations necessitating hospitalization only increased in the subgroup of patients with a history of exacerbations [19].

It should be noted that the data on the benefits of ICS in eosinophilic COPD is not so clear-cut. For example, 52-week-long FLAME study analysis results did not show significant differences in reducing exacerbation frequency or time to first exacerbation between eosinophilic and non-eosinophilic COPD patients treated with combinations of ICS and long-acting beta agonist or combination of long-acting beta agonist and long-acting muscarinic antagonist. [62].

It is necessary to consider the level of peripheral blood eosinophilia when starting long-term and safe ICS therapy. A meta-analysis of 10 clinical trials involving 10,861 patients revealed that COPD patients with low eosinophil levels (<2%) had a 31% higher risk of pneumonia compared to those with high eosinophil levels (≥ 2%) (HR=1.31, 95% CI - 1.06-1.62). Moreover, severe pneumonia was more common in COPD patients with low blood eosinophils. The tendency to increase the incidence of pneumonia with decreasing eosinophil levels persisted after stratification of patients by ICS use. In the ICS therapy group, pneumonia episodes were reported in 40 (3.8%) of 1063 patients with eosinophil levels <2% and in 48 (2.4%) of 2002 patients with eosinophil levels ≥ 2% (HR=1.53, 95% CI 1.01-2.31) [63].

In the retrospective ISOLDE study, there were more cases of pneumonia in those receiving fluticasone propionate (15/263 (5.7%)) in the <2% eosinophil group as compared to the placebo group (3/242 (1.2%)). However, in patients who had higher eosinophil levels, the rate of pneumonia did not differ significantly between both treatment groups: 5/107 (4.7%) for fluticasone propionate and 6/126 (4.8%) for placebo. Comparable results were observed for severe pneumonia: 4.6% treated with fluticasone propionate and 0.8% treated with placebo experienced a severe pneumonia in the eosinophil <2% group, compared to 3.7% and 4.8% in the eosinophil ≥ 2% group [64].

According to the 4-year UPLIFT study, the use of ICS in COPD patients corresponded with an increased risk of pneumonia compared to no ICS use: the hazard ratio of 1.33 (95% CI 1.00-1.75; p = 0.046) [65].

In another meta-analysis, the risk of pneumonia-related events was shown to be significantly higher in patients with eosinophil counts ≥2% treated with ICS (RR, 1.969; 95% CI, 1.369-2.833; P<0.001). No significant differences were observed in those with eosinophil counts <2% (RR, 1.29; 95% CI, 0.888-1.879; P<0.181). The analysis also suggested that a threshold of 2% for blood eosinophils may help determine the response to ICS treatment in COPD patients but could also predispose the patient to develop pneumonia [66].

Conclusion

COPD with eosinophilic inflammation is a distinct disease phenotype with its own characteristic clinical features. Around 25% to 40% of COPD patients exhibit eosinophilic inflammation, and approximately 28% of COPD exacerbations are linked to airway eosinophilia. A number of cytokines acts in the development of eosinophilic inflammation in COPD, among which IL5 is a key one.

Determinations of blood eosinophil counts, sputum analysis and induced sputum are common methods, with blood eosinophilia becoming a potential universal marker. However, the role of other markers, including those in sputum, is not completely understood. The impact of eosinophils on exacerbations and prognosis is a topic of debate, with conflicting data available. Glucocorticosteroids are essential in the treatment of eosinophilic COPD, but concerns about the risk of pneumonia need careful consideration. Identifying patients who may respond to glucocorticosteroids remains a challenge. Overall, the identification of the eosinophilic phenotype of COPD is crucial because it details the clinical characteristics of the condition and justifies the use of ICS.

Author Contributions:

Conceptualization, A.A. and M.A.; methodology, N.L. and A.P.; investigation, A.A. and M.A.; resources, A.A.; data curation, S.S. and M.M.; writing – original draft preparation, A.A., S.S. and M.M.; writing – review and editing, N.Z.; visualization, S.S. and M.M.; supervision, N.L. and N.Z. All authors have read and agreed to the published version of the manuscript.

Disclosures: There is no conflict of interest for all authors.

Acknowledgments: None.

Funding: None.

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