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LETTER TO THE EDITOR

In reply: response to Al-Kassimi and Alhamad

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I read with great pleasure the comments from Professor Feisal A. Al-Kassimi and Dr Esam H. Alhamad, and am willing to respond to them.

Although chronic obstructive pulmonary disease (COPD) has no specific symptoms and signs, COPD is a clinical diagnosis in that it requires the presence of symptoms and/or exposure to risk factors, with persistent airflow limitation [1]. It is now widely recognized that COPD is not a single disease but a syndrome, encompassing a heterogeneous group of conditions that share the defining characteristic of chronic airflow limitation [2]. A variety of terms have been used to describe specific subgroups or phenotypes of COPD, and there is still no consensus on the number and definition of different COPD phenotypes. We therefore classified potential COPD phenotypes on the basis of clinical, physiological, and radiological characteristics [3]. We then reviewed their association with clinically meaningful outcomes.

We used the term "overlap syndrome" to indicate a clinical phenotype which includes the group of patients with overlapping characteristics of asthma and COPD. The definition of overlap syndrome—the coexistence in patients of increased airflow variability with incompletely reversible airway obstruction—was adopted from a previous review article published in Thorax [4].

Professor Al-Kassimi stated that overlap syndrome is too heterogeneous to be accepted as a distinct COPD phenotype. However, the old ATS Venn diagram had already classified obstructive airway disease into 11 different syndromes, six of which were overlap syndromes [5]. Previous epidemiological studies showed that a substantial number of patients have combined clinical features of asthma and COPD [6–8], and recent cohort studies showed that these patients might have different prognoses [9–11]. These study results led to the consensus document on the COPD–asthma overlap phenotype which was published by the Spanish COPD experts group, who accepted overlap syndrome as a distinct clinical phenotype that may have a different natural history and prognosis [12].

Professor Al-Kassimi also stated that, because of its arbitrary definition, overlap syndrome is a "nonsyndome", and he worried that it could adversely affect phenotyping of COPD. However, consensus diagnostic criteria have been proposed for identification of the overlap phenotype. Major criteria include a strongly positive bronchodilator test (increase in FEV_1 ≥15 % and ≥400 mL), eosinophilia in sputum, and a personal history of asthma. Minor criteria include high total IgE, a personal history of atopy, and a positive bronchodilator test on two or more occasions. The overlap phenotype is diagnosed when two major criteria or one major and two minor criteria are met [12]. Furthermore, recent Spanish guidelines (GesEPOC) proposed COPD–asthma overlap as one of four clinical phenotypes that could potentially be incorporated into treatment guidelines [13, 14].

According to the comments of professor Al-Kassimi, "irreversible asthma" and "eosinophilic COPD" can be used as COPD phenotypes. Several studies have shown that COPD patients with sputum eosinophilia respond better to oral or inhaled corticosteroids [15–17]; however, whether controlling eosinophilic inflammation can modify disease progression and possibly affect mortality is unknown. The Spanish COPD experts group considered the term "eosinophilic COPD" as an alternative to the overlap phenotype, but rejected it because the name itself would require diagnostic tests not available at all health-care centers. We agree with their opinion, and believe that "eosinophilic COPD" can be regarded as an intermediate phenotype (endotype) of COPD rather than a clinical phenotype [18]. Many intermediate phenotypes have been proposed for COPD. However the precise relationships between them, and the appropriate

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therapeutic intervention, are still unclear. Therefore, these intermediate phenotypes need experimental validation [19].

Although several guidelines exist, the nosology of chronic obstructive airway diseases, including COPD and asthma, is still unclear [20]. Furthermore, there is substantial variation and uncertainty regarding use of the term "phenotype" in COPD. Undoubtedly, our potential COPD phenotypes and specific targeted therapy for each phenotype should be validated in further studies. The two phenotypes suggested by professor Al-Kassimi, irreversible asthma and eosinophilic COPD, can be regarded as part of the range of overlap syndrome. If it were found that these two phenotypes have distinct clinically-relevant outcomes different from those of overlap syndrome, they would be accepted as separate phenotypes.

Conflict of Interest Sang-Do Lee declares that he has no conflict of interest.

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