EDITORIAL

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Systemic White Blood Cell Count as a Biomarker for Chronic Obstructive Pulmonary Disease: Utility and Limitations

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Developing useful biomarker for chronic obstructive pulmonary disease (COPD) is a very important task on which many researchers have worked for a long time period. Such biomarkers can be used for assessment of disease status or disease activity, prediction of clinical outcome, and choice of therapeutic options. The strong need for developing biomarkers for COPD is originated from heterogeneity of the disease, scarcity of effective clinical tools for assessing clinical activity of the disease, and limited therapeutic options.

There are some specific blood biomarkers for predicting lung function decline, acute exacerbation, or even mortality from big longitudinal cohort studies. However, their performance is depressing[1]. Most of these biomarkers investigated up to date show relatively weak predictive power. They also have also critical limitations such as high cost, poor replicative power, difficulty to perform, and sometimes invasive. To accelerate COPD biomarker research, COPD Biomarker Qualification Consortium was established in 2011[2]. Through many studies, several blood biomarkers have demonstrated prediction potential for various clinically relevant outcomes. C-reactive protein, fibrinogen, leukocytosis, interleukin 6, surfactant protein D, Clara cell protein-16, and adiponectin are leading candidates. However, none of these is satisfactory for clinical use even after demonstrating strong statistical power because of their very suboptimal performance.

Koo et al.[3] demonstrated possible correlation of systemic white blood cell (WBC) count and the quality of life (QoL) or lung function in COPD patients. Peripheral blood leukocytosis has already been well investigated in the aspect of inflammatory biomarkers for COPD, showing no definite correlation with lung function decline[4], possible prediction of acute exacerbation[5], and mortality[6]. Actually, systemic WBC count did not show significant correlation with QoL in this study[3]: the difference according to WBC quartile (p=0.90 for Euro quality of life instrument [EQ5D] index, p=0.51 for EQ5D visual analogue scale) or association between WBC count and EQ5D index (p=0.58) did not reach statistical significance. When systemic WBC count was analyzed according to smoking status, it showed significant correlation with EQ5D index in non-current smokers (p=0.01).

There was somewhat correlation between WBC count and pulmonary function variables. However, the significance level was relatively weak (for forced vital capacity, p=0.045 and for forced expiratory volume in 1 second [FEV_1] %, p=0.051). Even in current smoking patients, the significance became lost. These differences according to the smoking status might provide additional information for treatment selection according to various phenotypes in the future if additional proof is accumulated.

Current smoking increases serum WBC count even after adjusting for genetic background[7]. In Koo et al.'s study[3], systemic WBC count was higher in more severe COPD patients only in the non-current smoking group. The mechanism was not fully understood yet. Current smoking itself could have more powerful effects on WBC count compared to COPD severity and comorbid conditions.

The strength of this study is that it used data of Korean National Health and Nutrition Examination Survey (KNHANES), a nationally representative, population-based survey. It could represent the general population, thus reflecting the "real

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world" aspect. Therefore, it might avoid selection bias that most large sized and longitudinal cohort studies might have. Many famous studies have been performed under strict inclusion and exclusion criteria such as preset lung function criteria usually enrolling moderate to very severe patients without significant co-morbid conditions. As a result, they might not reflect the "real world" when results of those studies should be applicable for individual patient's treatment.

Another strength of the study is its relatively large size with well-matched control. It included 1,227 COPD patients and 8,679 non-COPD controls. As comparison, the famous multinational study "ECLIPSE" included about 2,000 COPD patients without non-COPD healthy controls. In the aspect of COPD severity, there is another significant difference. ELIPSE included GOLD 2 (44.2%), GOLD 3 (42.1%), and GOLD 4 (13.7%) patients. However, KNHANES included GOLD 1 (44.8%), GOLD 2 (50.2%), GOLD 3 (4.5%), and GOLD 4 (0.5%) patients. It is probably due to the fact that most clinical studies are aimed at patients with symptomatic GOLD 2 or more. WBC is not associated with basal pulmonary function in the COPD cohort study with moderate to severe stage like ECLIPSE. However, in this general population study including 45% of mild COPD patients, WBC showed correlation with basal lung function to some extent. Therefore, there could be a suspicion that WBC might affect lung function especially at the early phase of COPD.

This study also has several limitations. First, pulmonary function test performed in KNHANES did not include bronchodilator test. Therefore, post-bronchodilator FEV_1 could not be measured and some portion of asthma patients could be included. Second, KNHANES did not include delicate interview about the patient's respiratory symptoms or longitudinal follow-up including acute exacerbation, change of subjective dyspnea, or lung function. Therefore, we could not confirm that the blood sample was drawn at a very stable state. Furthermore, KNAHES included only general health related quality of life score EQ5D as reference instead of Saint George Respiratory Questionnaire. There was no direct comparison study of EQ5D with COPD assessment test or modified Medical Research Council dyspnea score. In addition, EQ5D reflected "general" QoL rather than "COPD-associated" QoL. Another problem of this study is at the statistical issues the authors have processed. Authors suggested that there was correlation between WBC and EQ5D scores. However, multivariate analysis was performed including age, gender, COPD severity, and comorbidities in the absence of statistical significance to confirm direct correlation between crude WBC and EQ5D scores. It is difficult to interpret the meaning of multivariate analysis, including other variables already known to be correlated if EQ5D is already confirmed to be associated with comorbidities and COPD severity. Therefore, statistical analysis needs to be reviewed again. For another issues, in this study, WBC counts were usually within the normal range. Investigation was done with quartiles distribution and the cut-off point could not be established when these results were applied to general patients. In addition, the statistical power seemed to be weak. There has been issues about the clinical translation of biomarkers even when they have very good statistical power[8].

KNHANES only included complete blood test without WBC differentials. Recently, blood eosinophil count, fraction of eosinophil, neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio are under active investigation because they are also important surrogate markers in treatment selection according to COPD phenotype. No additional information is available on the use of inhaled steroids, which have been controversial in recent years[9].

In conclusion, authors suggested that systemic WBC count in COPD could be used as a prognostic biomarker based on findings that a high WBC count was related to poorer lung function and lower quality of life. It seemed to be meaningful because they suggested the correlation of WBC count with COPD clinical parameter based on KNHANES, a large-scale population-based health and nutritional survey performed by the Korean Centers for Disease Control and Prevention. There is a limitation that correlations of systemic WBC counts with quality of life or pulmonary function were relatively weak. However, unlike existing cohort studies, this study included large proportion of mild COPD patients and it could reflect "real life setting" COPD. If acquisition of additional test results such as leukocyte fraction and longitudinal clinical data are allowed, choice of therapeutic option including inhaled corticosteroid could be made for Korean COPD population.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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