## Pulmonary Hypertension: A Predictor of Lung Cancer Prognosis?

*To the Editor*:

With interest, we read the paper by Eul and colleagues (1), which confirms the previous finding that pulmonary hypertension (PH) is present in a significant proportion of patients with lung cancer. Moreover, this is the first report to show that the presence of PH has a marked impact on the clinical outcome, including survival, of patients with lung cancer. The underlying mechanism is likely of the interaction between tumor cells and endothelial cells, which initiates clot formation and releases cytokines to initiate macrophage recruitment, intimal proliferation, and ultimately PH, which is the feature of pulmonary tumor thrombotic microangiopathy (2). In addition, cancer therapies may induce pulmonary arterial hypertension (PAH). Dasatinib, which is one of the tyrosine kinase inhibitors used as a drug for the treatment of tumors, has been reported to cause direct pulmonary artery endothelial cell toxicity through the production of mitochondrial reactive oxygen species (3).

Both $FEV_1$ and $DL_{CO}$ were significantly lower in the group with pulmonary artery/aorta (PA/A) $>1$ in this study, and the computed tomographic signs of emphysema did not differ between the groups. Therefore, the authors suggest, it may be difficult to discern whether this significant decrease is due to the presence of PH or not. However, we do not quite agree with this point of view. That is, some patients in this study had pulmonary function and echocardiography, 495 patients had $FEV_1$ results, and 494 patients had $FEV_1$/FVC results. We can use these data to determine whether patients are accompanied by chronic obstructive pulmonary disease (COPD) and the severity of COPD. In this research, 132 patients with lung cancer have echocardiographic pulmonary artery systolic pressure data, and we can analyze the correlation between echocardiographic pulmonary artery systolic pressure, $FEV_1$, and $DL_{CO}$ in some patients who have also done lung function and echocardiography to find out whether the decrease of $FEV_1$ and $DL_{CO}$ is related to PH. In this way we can determine whether it is PH or more severe COPD that predicts increased mortality in patients with lung cancer. In addition, all COPD-related lung diseases (such as interstitial lung disease, bronchiectasis, sleep apnea, etc.) are additional possible confounders in the development of PH (4). Interestingly, PA diameter and PA/A have previously been shown to be associated with increased mortality in patients with COPD. It is known that the severity of COPD as measured by $FEV_1$ is an independent predictor of mortality (5).

Eul and colleagues hold the view that such broadening of the database of putative lung cancer–associated PH is mandatory before interrogating whether to use a treatment of PH with available PAH because approved drugs might provide a new therapeutic option in some of these patients (e.g., those with most pronounced PH) (1). However, we do not agree with this view either. In patients with lung cancer, once there is a significant increase in pulmonary artery pressure, it is necessary for them to check for other diseases, such as lung disease, left heart disease, chronic thromboembolic PH, and PAH. In addition to patients with PAH, lung disease and/or hypoxia-induced PH are mainly targeted at the treatment of primary disease (such as COPD, etc.), in which long-term oxygen therapy is recommended, whereas routine targeted drug therapy is not recommended (6).

Despite our reservations, the research by Eul and colleagues (1) offers novel evidence suggesting possible increased prevalence of PH in patients with lung cancer. The research also indicates that PH is associated with poor survival in patients with lung cancer. It is precisely because of the inseparable relationship between lung cancer and PH that a prospective multicenter study based on right cardiac catheterization is important to confirm the prevalence of PH in patients with lung cancer, which is also significant to the prognosis of lung cancer. ■

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## Reply to Zheng *et al.*

*From the Authors*:

We appreciate the authors' interest and response to our work (1). We agree with the authors that chronic obstructive pulmonary disease (COPD) is an important and prevalent comorbidity in patients with lung cancer. Moreover, the concern raised that the survival difference we observed might be linked to COPD rather than to pulmonary hypertension (PH) may be valid (2). For this purpose, we calculated the impact of COPD, specifically $FEV_1$ and $FEV_1$/FVC, on the survival of patients with lung cancer using the Cox proportional hazard survival model. Notably, no significant impact of $FEV_1$ and $FEV_1$/FVC on progression free survival (PFS) and overall survival (OS) was observed in our cohort of patients with lung cancer (Figure 1). Although the data may be insufficient to claim the absence of any effect of $FEV_1$ or $FEV_1$/FVC on PFS or OS, this finding remarkably differs from the strong correlation between PFS/OS and pulmonary artery size (PA), and pulmonary artery to ascending aorta ratio (PA/A ratio) that we noted in the same patient cohort. In addition, we recalculated our Cox proportional hazard survival model after adjusting for $FEV_1$ and $FEV_1$/FVC. Importantly, even after adjusting for $FEV_1$ and $FEV_1$/FVC, our data set is sufficient to conclude that median OS is significantly reduced in patients with a PA size $\geq$ 28 mm ($P = 0.023$) and PA/A ratio $\geq 1$ ($P < 0.001$). In conclusion, we believe that our data set provides strong evidence that an increased PA/PA/AA ratio, probably indicating PH, is the main predictor of survival in this lung cancer cohort.

In addition, to assess left heart diseases as a confounding factor for PH in patients with lung cancer, we would also like to emphasize that we already evaluated criteria of left heart disease in our study (1). As an example, we were not able to find any statistically significant difference in left ventricle ejection fraction between PA/A ratio $> 1$ and PA/A ratio $\geq 1$. This makes systolic left heart disease unlikely as the cause of our findings.

We agree with the authors that we first have to gather more insight on the causes of PH in lung cancer before we may consider treating patients with lung cancer for PH. To consolidate these findings, we are currently conducting a clinical trial (NCT04467333). ■

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