Response to: ' Correspondence on 'Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension" by Iudici *et al*

In their correspondence Iudici *et al*[1] highlight three important aspects which are to consider in the interpretation of survival data when introducing new thresholds of an early stage of disease.[2] They point out, that lead-time bias, length-time bias as well as increasing numbers of patients have to be considered for the new haemodynamic definition of pulmonary arterial hypertension (PAH).

In studies investigating the effect of systematic PAH screening programmes on survival in patients with systemic sclerosis, part of the effect of an increased survival may be attributed to lead-time bias and length-time bias.[3 4]

We agree with Iudici *et al* that lead-time bias is an important aspect when introducing a new definition of a disease, which includes patients at a less severe stage. This becomes especially important for screening programmes, as survival of screened patients who are diagnosed at early disease stages may implicitly be better compared with patients with a more severe disease.

In our study we analysed the frequency of PAH in patients with systemic sclerosis when applying the new PAH definition according to the suggestion from the World Symposium on pulmonary hypertension in Nice 2018. According to a large meta-analysis of haemodynamic data of healthy people, a pulmonary vascular resistance (PVR) >2 Wood Units (WU) can already be seen as abnormal in most age levels, with regard to mean PVR +2 standard deviations.[5] We introduced the threshold of a PVR of 2 WU to investigate, whether these patients already present with pathological characteristics of pulmonary vascular disease.

We would like to emphasise that the objective of our study was not to present an advantage of early diagnosis, as our data does not provide enough information to investigate this question. We aimed to show, that even patients with less severe changes of pulmonary vascular haemodynamics already showed typical characteristics of pulmonary vascular disease and an impaired survival, though part of these patients will never develop manifest PAH. The higher the lead-time bias with increased survival-time for these patients would be, the less pronounced would be the difference of survival between patients with PVR ≥2 WU compared with PVR <2 WU. A difference of survival between these two groups therefore supports the hypothesis, that patients with PVR ≥2 WU are already compromised.

Prediction of manifest PAH is, as Iudici *et al* correctly state, complicated and multifactorial. Statistical models have not yet been implemented and assumptions may possibly be unrealistic. Though determining factors for the development of manifest PAH have already been identified in PAH, prediction of the disease is still not straight-forward and needs further investigation. Furthermore, considering several known determining factors of survival or progression to manifest disease in this cohort would most likely lead to overfitted models, as simple sizes in our cohort were restricted due to the rarity of both systemic sclerosis and PAH. However, the sensitivity analysis of an age-adjusted Cox regression which we performed in our study confirmed our findings of a significant impact of PVR on survival. As the applied risk stratification models also seemed to work better with patients with PVR ≥2 WU, but not for PVR <2 WU, their use in clinical practice would also be appropriate in this patient group.

Therapeutic indications in a cohort of patients with mild pulmonary vascular disease who usually would only be diagnosed with manifest PAH due to a change in definition should be carefully investigated, as data on PAH-targeted treatment in these patients is currently lacking. In this regard, the meaning of a diagnosis of mild PAH should be handled with care regarding its therapeutic consequences and impact on the patient.

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