

Correspondence on 'Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension'

The 6th World Symposium of pulmonary hypertension has proposed to widen the definition of pulmonary arterial hypertension (PAH) identifying a lower cut-off for mean pulmonary arterial pressure (mPAP) from ≥ 25 mm Hg (as recommended by the actual guidelines) to > 20 mm Hg, in combination with pulmonary vascular resistance (PVR) ≥ 3 Wood units (WU).

In general, a change in the formal definition of a disease can impact in many different ways how the patients are identified, treated, and their prognosis. One of the consequence of such redefinition in patients with systemic sclerosis (SSc) has been addressed by Xanthouli *et al*, in their very interesting and original paper.¹ The authors have shown that since most patients with SSc with an mPAP 21–24 mm Hg have PVR < 3 WU, if left unmodified, the new criteria could allow to reclassify as PAH only 8% of mPAP 21–24 mm Hg patients, despite they display a pulmonary vascular disease and a poor prognosis. This paper, focusing on one aspect related to disease redefinition, has prompted us to add further general comments on what we should consider when future observational research will compare samples of patients identified by a more strict (current criteria for PAH in this case) or broader (new proposed criteria) disease definition, keeping in mind that the latter group include by definition (a) a larger number of patients, (b) likely to receive a diagnosis earlier and (c) with an average milder disease.

First, the validity of survival analyses comparing cohorts of patients defined according to an 'old' versus a 'broadened new' definition can be threatened if biased analyses are performed. Let's assume we want to compare the survival of patients with SSc-PAH diagnosed according to the current (figure 1, patient 1) versus the new proposed criteria (figure 1, patient 2) in an observational setting, hypothesising that the true survival time and mPAP evolution over time of both patients are exactly the same. Assuming that the screening strategies to select patients with SSc for right heart catheterisation remain the same over time, patient 2 will likely receive a diagnosis of PAH earlier. If we calculate the survival time from the date of diagnosis, an additional time period is added by the use of new criteria, which is the time during which mPAP increased from 21 mm Hg (lower limit of the proposed new definition) to 25 mm Hg (the lower limit of the current definition), which is called lead time. For a fair comparison of survival, this time period should be discarded from the survival time of patient 2.^{2,3} If we do not adjust for the lead time, we can erroneously estimate a longer survival for patients 2 compared with that of patient 1. This phenomenon is well known in cancer screening.^{4,5}

Therefore, the comparison of survival involving 'old' and 'new' definitions of PAH should be conducted using adequate methods to correct lead time bias. This can be performed by subtracting an estimate of the lead time bias obtained in a multi-state model with simple—possibly unrealistic—assumptions,⁵ or more complex models of the mPAP measurement process, akin to the use of tumour growth models in cancer screening.⁶ Models adjusted for the age, and/or calendar-matched population can also allow to overcome this potential problem.

Second, by using the new criteria, PAH cohorts will include also patients with lower values of mPAP, who are less ill, and

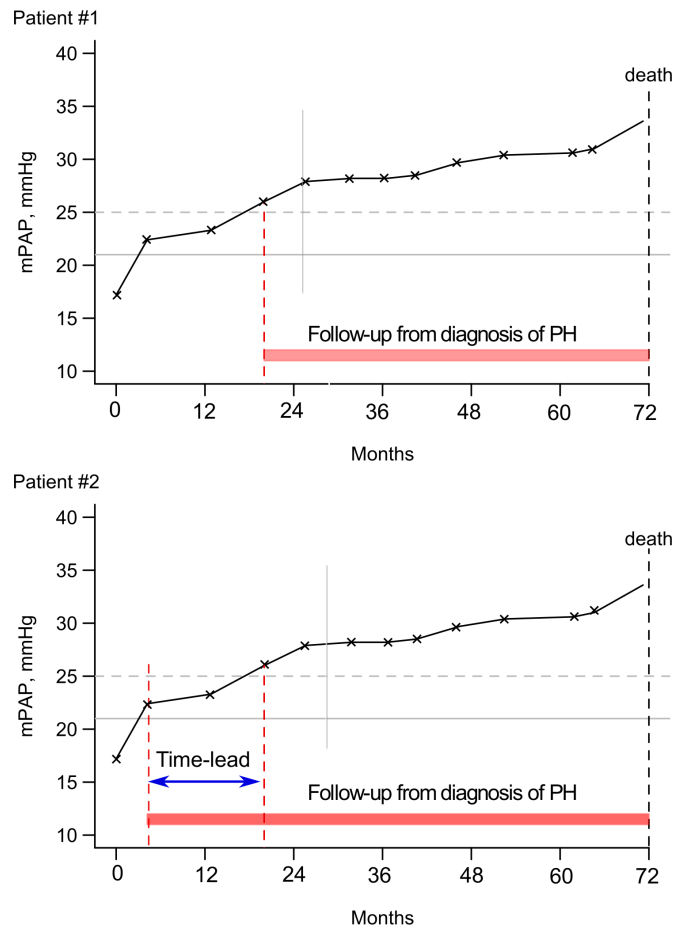


Figure 1 Lead time bias. Each patient survived the same time from an equivalent starting point of mean pulmonary arterial pressure (mPAP). Illustration of a lead time bias occurring when survival time is calculated from the diagnosis according to the current (patient 1), or the new proposed (patient 2) criteria for the diagnosis of pulmonary hypertension (PH).

would not necessarily develop a severe disease in the short-term and mid-term. Actually, studies on patients with SSc with borderline PAH (mPAP between 21 and 24 mm Hg) have shown that an increase of mPAP above 25 mm Hg only occurs in about one-third of cases within 5 years.^{7,8} Therefore, the simple incorporation in the 'diseased' group of patients with a milder PAH, although already having a clinically meaningful pulmonary vascular disease, right ventricle dysfunction and reduced long-term survival,⁹ dilutes the disease severity of the 'redefined PAH' group. This aspect should be considered in order not to artifactually ascribe to the new diagnostic strategy a causal link with the observed better outcome.

Finally, even if in the context of SSc this proposed new definition is likely to reclassify a small number of patients as having PAH,^{1,10} an increased PAH prevalence/incidence recorded in next years, even limited, is expected, and should be interpreted in the context of this lower threshold for diagnosing PAH.

In conclusion, practical and methodological aspects can arise from a disease redefinition, ranging from the risk of not including all patients potentially taking benefit from receiving a diagnosis earlier as shown by Xanthouli *et al*,¹ to the potential pitfalls that can occur in observational research carried out in patients identified by different criteria.

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