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Outcomes of patients with decreased arterial oxyhaemoglobin saturation on pulmonary arterial hypertension drugs

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Summary of the "take home" message: A significant decrease in arterial oxyhaemoglobin saturation is relatively common at first reassessment of patients treated with pulmonary arterial hypertension drugs. Such a decrease in arterial oxyhaemoglobin saturation is associated with poorer outcomes.

This article has supplementary material online, which is accessible from the issue's table of content online at https://erj.ersjournals.com.

Abstract

Rationale: Drugs approved for the treatment of pulmonary arterial hypertension (PAH) improve long-term outcomes. These drugs have pulmonary vasodilator properties which may potentially cause a decrease in arterial oxyhaemoglobin saturation (SaO_2) in some patients.

Objectives: The present retrospective study of the French PAH Registry aimed to describe clinical characteristics and outcomes of patients showing a $\geq$ 3% decrease in SaO_2 while treated with PAH drugs.

Methods: We reviewed 719 PAH patients. The exclusion criteria were PAH associated with congenital heart disease and PAH with overt features of venous/capillaries involvement.

Main Results: One hundred and seventy-three (24%) patients had a $\geq$ 3% decrease in SaO_2. At diagnosis, they were older, with a lower diffusion capacity for carbon monoxide and a shorter 6-minute walk distance, when compared to those who did not display a $\geq$ 3% decrease in SaO_2. The percentage of patients meeting the ESC/ERS low risk criteria at re-evaluation was significantly lower in those with a $\geq$ 3% decrease in SaO_2 and more patients started long-term oxygen therapy in this group (16% versus 5%, $p<0.001$). A $\geq$ 3% decrease in SaO_2 was associated with a poorer survival (Hazard Ratio 1.81 :95% confidence interval 1.43-2.34; $p<0.0001$). In a multivariate Cox analysis, a $\geq$ 3% decrease in SaO_2 was a prognostic factor independent of age at diagnosis and ESC/ERS risk stratification at follow-up.

Conclusions: When treated with PAH drugs, a large subset of patients experience a $\geq$ 3% decrease in SaO_2, which is associated with worst long-term outcomes and reduced survival.

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Keywords: Pulmonary arterial hypertension; arterial blood gas; Hemodynamics; Treatment

Introduction

Pulmonary arterial hypertension (PAH) is characterized by progressive and sustained increase in pulmonary vascular resistance leading to exercise limitation, right heart failure and death (1). PAH therapy targets three pharmacological pathways and offers the possibility of prescribing mono, dual or triple therapy, depending in particular on the severity assessed by a risk stratification strategy (1). All currently approved PAH drugs are pulmonary vasodilators (2).

In PAH, pulmonary vascular remodelling and loss of pulmonary capillary surface are responsible for increased pulmonary vascular resistance (3). In addition, there is an increase in pulmonary vascular tone contributing to preserve gas exchanges (4). Therefore, any vasodilator acting on the pulmonary circulation can cause an increase in the perfusion towards not optimally ventilated areas which may lead to a worsening of pulmonary gas exchanges (5). When PAH patients respond well to medical therapy, this potential side effect is compensated by the increase in cardiac output which leads to an increase in mixed venous oxygen content (6). By contrast, the worsening of pulmonary gas exchanges may be greater in patients with co-morbidities. Indeed, even if a well-characterized chronic respiratory disease rules out the diagnosis of PAH, many patients with idiopathic PAH may present with some degree of airways disease, or with mild pulmonary interstitial abnormalities (7). This proportion of patients with lung involvement is even larger in PAH associated with connective tissue disease such as systemic sclerosis. Such patients are likely to experience worsening of arterial blood gases after initiation of PAH drugs. The first large multicentre PAH Registry published in 1987 showed that the majority of patients with idiopathic, heritable and drug-induced PAH presented with hypoxemia and hypocapnia at the time of diagnosis (8). A more recent study confirmed that most idiopathic PAH patients had mild hypoxemia and hypocapnia (9). It should be remembered that current guidelines suggest

performing arterial blood gases at baseline and at reassessment visits, but they can be replaced by a measurement of pulse oxygen saturation (SpO_2) in stable patients (10).

We analysed arterial blood gases at the time of diagnosis and after 3-12 months of follow-up in a large number of PAH patients from the French Registry. We aimed to determine the proportion of patients with a decrease of 3% or more of arterial oxyhaemoglobin saturation (SaO_2) while treated with PAH drugs and to describe clinical characteristics and outcomes of these patients.

Methods

Additional details on the patients, measurements and statistical analysis are available on the online supplementary material.

We reviewed all incident patients who were enrolled in the French Registry between April 2008 and April 2019. The *Commission Nationale Informatique et Liberté* approved the methods used to collect and analyse registry data on May 24, 2003 (approval number 842063).

Expert centres of the French Registry were instructed to classify patients at multidisciplinary meetings using the most recent diagnostic algorithm. All patients with significant lung function abnormalities or parenchymal lung disease on computed tomography of the chest were excluded. Patients were included retrospectively in the present study if they had a diagnosis of PAH, and a re-evaluation within 12 months of diagnosis after having received at least one PAH drug between baseline and re-evaluation and having had a right cardiac catheterization and arterial blood gases while breathing room air at both visits. The hemodynamic definition of pre-capillary pulmonary hypertension used was that of the 2015 ESC/ERS guidelines (10). Patients with PAH associated with congenital heart disease and PAH with overt features of venous/capillaries involvement (pulmonary veno-occlusive disease / pulmonary capillary haemangiomatosis) were excluded (11). Although there were no

precise specifications for prescribing long-term oxygen therapy throughout patient follow-up, the recommendations were to start this treatment if PaO_2 in a stable state patient was less than 60 mmHg.

Partial pressure of oxygen (PaO_2) and of carbon dioxide ($PaCO_2$) in arterial blood without supplemented inspired oxygenation are available in a large subset of patients. Conversely, arterial oxyhaemoglobin saturation was not available in the Registry. Therefore it was calculated using the Severinghaus' equation; $SaO_2=(((PaO_2{}^3+150\ PaO_2)^{-1} \times 23{,}400)+1)^{-1}$ (12). Alveolar-arterial oxygen partial pressure difference ($PA\text{-}aO_2$) was calculated according to the following equation: $PA\text{-}aO_2=(150-PaCO_2/0.8)-PaO_2$.

The ESC/ERS guidelines risk stratification table was used according to the French Registry invasive and non-invasive approaches, as previously described (10, 13).

Statistical analysis

All analyses were performed using SAS R9.4 TS1M6 (SAS Institute, Cary, NC, USA). The significance level was set to $p<0.05$.

Continuous parameters were displayed as mean (standard deviation) and categorical factors as frequency (percent). Univariate comparisons of patients according to the decrease in $SaO_2 \geq 3\%$ at re-evaluation were carried out using the Mann-Whitney test for the former and the Chi-Square test or Fisher's exact test when appropriate for the latter.

The association between a $\geq 3\%$ decrease in SaO_2 at re-evaluation compared to baseline and, first the identification of baseline factors associated with SaO_2 decrease and, second transplantation-free survival, were analysed using logistic regression and Cox proportional hazards model, respectively.

The cut-point in decrease in SaO_2 was chosen empirically from a pilot study (see methods and figure S1 on the online supplementary material). Three percent or more decrease SaO_2 as cut-point was validated *a posteriori* as the best risk stratification factor selected using concordance probability and point closest-to-[0,1] corner in the ROC plane (14).

Results

Baseline characteristics of the study population

From April 2008 to April 2019, 3483 PAH patients with idiopathic, heritable, drug-induced, connective tissue disease-associated, porto-pulmonary or HIV-associated disease were enrolled. Among them, the study population consisted of 719 patients reassessed within 12 months with right heart catheterization and arterial blood gases (Figure 1). At baseline, mean age was 60 ± (SD) 14 years, 57% of the patients were women and most patients were in WHO/NYHA functional class III (60%) or IV (12%). The most frequent diagnosis was idiopathic PAH (39% of the study population). The comparison of the characteristics of the 719 patients included in the analysis to the 2764 excluded patients shows that the two groups were broadly similar (Online supplementary table S1).

Distinctive features of patients with a ≥ 3% decrease in oxyhaemoglobin saturation

Distinctive features at baseline

The median time between baseline and re-evaluation was 5 (interquartile range (IQR): 4 -6) months. At re-evaluation, 173 (24%) patients had a ≥ 3% decrease in SaO_2 compared to baseline. Comparisons of demographic, functional and hemodynamic data at baseline of patients with a ≥ 3% decrease in SaO_2 and patients with a < 3% decrease in SaO_2 are shown in table 1. More patients had a diagnosis of PAH associated with connective tissue disease among patients who had a ≥ 3% decrease in SaO_2 at re-evaluation (33% versus 23%;

p=0.008). Conversely, less patients had a diagnosis of porto-pulmonary hypertension (12% versus 21%; p=0.007). Patients who had a ≥ 3% decrease in SaO_2 at re-evaluation were older (64 ± 12 years versus 58 ± 15 years; p<0.0001) and walked a shorter 6-minute walk distance (6MWD) (272 ± 147 m versus 314 ± 151 m; p=0.005) at baseline. Diffusing capacity of the lungs for carbon monoxide (DL_{CO}) was significantly lower at baseline in these patients (42 ± 17 % of pred. versus 51 ± 20 % of pred.; p<0.0001). Regarding haemodynamic, the only difference between groups was a slightly lower mean pulmonary artery pressure (mPAP) among patients with a ≥ 3% decrease in SaO_2 (44 ± 9 mmHg versus 47 ± 12 mmHg; p=0.033).

Distinctive features at re-evaluation

The comparisons of changes between diagnosis and reassessment of clinical, functional and hemodynamic characteristics depending on the presence or not of a ≥ 3% decrease in SaO_2 are shown in table 2. The proportion of patients who improved their WHO/NYHA functional class compared to those who had WHO/NYHA functional class unchanged or impaired at re-evaluation was significantly lower in the group with a ≥ 3% decrease in SaO_2 (p=0.031). The improvement in the 6MWD at re-evaluation over baseline was significantly lower among patients with a ≥ 3% decrease in SaO_2 (+27 ± 103 m versus +51 ± 120 m; p=0.046). The mean value of DL_{CO} decreased slightly in patients with a ≥ 3% decrease in SaO_2 and remained stable in patients without a significant decrease in SaO_2. The hemodynamic changes with PAH drugs were similar between the two groups of patients except for right atrial pressure and mPAP which improved slightly less in patients with a ≥ 3% decrease in SaO_2.

PAH drugs

Initial therapy prescribed at baseline in the study population consisted of an endothelin receptor antagonist in 65% of patients, a phosphodiesterase type 5 inhibitor in 63%, a prostacyclin analogue in 6%, riociguat in one patient, and selexipag in one patient. All patients received at least one PAH drug before re-evaluation, and 39% and 6% of the study population had double and triple combination therapy, respectively. Nine percent of patients were also treated with a calcium channel blocker. No statistically significant differences were observed regarding calcium channel blocker use, double or triple PAH therapies between the two groups of patients (data not shown). Twenty-six and 23% of patients treated with an endothelin receptor antagonist and with a phosphodiesterase type 5 inhibitor (combined or not with another treatment of PAH for both class of drugs) had a decrease of 3% or more in SaO_2, respectively. There were 88 patients with a ≥ 3% decrease in SaO_2 at re-evaluation on monotherapy, 47, 38 and 3 were on an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor and a prostacyclin analogue, respectively.

Prognostic value of a ≥ 3% decrease in oxyhaemoglobin saturation

The percentage of patients at re-evaluation in a low-risk status (invasive approach as defined above) was significantly lower in the group of patients with a ≥ 3% decrease in SaO_2 compared to patients with less than 3% decrease in SaO_2 (26% versus 47%; $p<0.0001$). By taking brain natriuretic peptide (BNP) or N-terminal prohormone brain natriuretic peptide (NT-proBNP) instead of right atrial pressure and cardiac index to define low-risk status, the difference was also significant between the two groups (28% versus 45%, $p=0.002$) (Online supplementary table S2). Between baseline and re-evaluation, more patients started long-term oxygen therapy among patients with a ≥ 3% decrease in SaO_2 (16% versus 5%; $p<0.0001$), whereas a similar percentage of patients stopped this therapy (1% versus 3%, p=0,38). Almost

twice as many patients as a percentage were already on oxygen therapy at the time of reassessment in the group with a 3% or more drop in SaO_2 compared to those who did not have this drop in SaO_2. The figures were 50% (87/173) versus 28% (155/546), respectively ($p < 0.001$).

Over a median (IQR) follow-up of 3.3 (1.9 - 5.0) years, 85 (49%) patients died and 6 (3%) underwent lung transplantation among patients with a $\geq$ 3% decrease in SaO_2 compared to 176 (32%) and 14 (3%) in patients with less than 3% decrease in SaO_2, respectively (Logrank test $p<0.0001$) (Figure 2). In sensitivity analyses, excluding patients with PAH associated with connective tissue disease, portal hypertension and HIV infection, as well as keeping only patients with idiopathic PAH, we obtain similar results (Online supplementary tables S3 and S4, and figure S2). Results of the univariate Cox regression analysis which determines the relation between transplantation-free survival and covariates assessed at baseline and re-evaluation are shown in table 3. Having a SaO_2 drop $\geq$ 3% at the time of first re-evaluation while on PAH therapy was associated with poorer transplantation-free survival. WHO/NYHA functional class III or IV, 6MWD $\leq$ 440m, right atrial pressure $\geq$ 8 mmHg, cardiac index < 2.5 L/min/m^2, BNP $\geq$ 50 ng/L or NT-proBNP $\geq$ 300 ng/L at re-evaluation were also associated with a poorer transplantation-free survival. A multivariate Cox analysis was performed with 579 patients including all covariates associated with survival in the univariate analysis ($p<0.05$), by eliminating BNP or NT-proBNP and DL_{CO} from the analysis because of significant attrition of the population. This analysis showed that a $\geq$ 3% decrease in SaO_2 at re-evaluation was independently associated with a poorer transplantation-free survival. By combining WHO/NYHA functional class, 6MWD, right atrial pressure and cardiac index to define the population not at low risk at re-evaluation, a $\geq$ 3% decrease in SaO_2 was still an independent prognostic factor in a multivariate Cox analysis (Hazard Ratio 1.54; 95% CI 1.13 - 2.10, $p = 0.007$) (Table 4). Conversely, upon incorporation of DL_{CO} into the Cox model in a

restricted population of 379 patients, a ≥ 3% decrease in SaO_2 at re-evaluation was no longer independently associated with transplantation-free survival (Online supplementary table S5).

Exploratory analysis of factors associated with a ≥3% decrease in SaO_2

Alveolar-arterial oxygen partial pressure difference increased in patients with a ≥ 3% decrease in SaO_2 whereas it decreased in patients with less than 3% decrease in SaO_2 (+16 ± 12 mmHg versus -6 ± 14 mmHg; $p<0.0001$). No significant change in $PaCO_2$ was observed in any patient group. A weak correlation was observed between the change in SaO_2 and the change in DL_{CO} between baseline and re-evaluation (Online supplementary figure S3). Other correlations with the change of SaO_2 are shown in the online supplementary table S6. Two logistic regression models show that only the baseline DL_{CO} is an independent predictor of a ≥ 3% decrease in SaO_2 between baseline and reassessment (Online supplementary table S7).

Discussion

The main findings from our study are as follows. First, a relatively large number of patients with PAH experienced a ≥ 3% decrease in SaO_2 after a few months of treatment with PAH drugs regardless of the class of drugs used. These patients with ≥ 3% decrease in SaO_2 diagnosed with PAH according to current criteria, differed at the time of diagnosis by older age, lower DL_{CO}, and lower mPAP. Third, the occurrence of a significant decrease in SaO_2 was associated with worse outcomes. Finally, the significant decrease in SaO_2 under treatment was linked to a low DL_{CO}.

We decided to study SaO_2 for two main purposes. First, SaO_2 is a more important determinant of oxygen delivery than PaO_2. Given that haemoglobin is normal (which is most often the case in PAH), a patient's SaO_2 and cardiac output are the two independent variables which

provide information about the amount of oxygen that is available to the tissues (15, 16). The other reason is that SaO_2 can be estimated by a pulse oximeter in a simple and non-invasive way in clinical practice unlike PaO_2. In fact, in our study we could not use SpO_2 values because measurement conditions in the database of the French Registry were not specified and arterial oxyhaemoglobin saturation from arterial blood gases was not a value to enter (only PaO_2 and $PaCO_2$ were collected). Therefore, SaO_2 had to be calculated from PaO_2 using the Severinghaus' equation in our study. It must be emphasized that it was shown that SaO_2 from the Severinghaus' equation is in excellent agreement with SaO_2 from arterial blood gases for values greater than 70% (12, 17). The relevance of the choice of a ≥ 3% decrease in SaO_2 was supported by determining the cut-point by the method described by Rota *et al*. (14) in a sensibility analysis of the present study. It should also be noted that the mean values of SaO_2 and PaO_2 reached at re-evaluation in the 173 patients with a ≥ 3% decrease in SaO_2 were 83 ± 8% and 51 ± 10 mmHg, respectively. Such low SaO_2 values may be associated with deleterious effects (15, 16, 18). Consequently, SaO_2 or SpO_2 measured at rest and in room air could be a useful tool and a ≥3% decrease in SaO_2 at re-evaluation seems to be a relevant cut-point value.

Twenty four percent of our study population had a ≥3% decrease in SaO_2 from a population of 719 patients with PAH. These 719 patients were included in the French Registry by following the diagnostic algorithm of the World Symposia since 2003 (19) and adapted according to the most recent conferences (11). All the patients came from expert centres, therefore, the risk of incorrectly classifying these patients in the clinical classification of pulmonary hypertension is very low. Compared to the REVEAL registry (20), our study population is similar in terms of the percentage of patients with idiopathic, heritable and associated PAH. In comparison with previous studies on PAH (13, 21) our population is

slightly older and had a few more comorbidities, with a high proportion of smokers or ex-smokers but comparable to one of these 2 studies (21). This can be explained by the fact that we included in our study all the patients of group 1 of the clinical classification of pulmonary hypertension (except congenital heart diseases) (11). Patients with systemic sclerosis or portal hypertension partly explain the differences of baseline data in our study population.

Our study gives some clues about the cause of decrease in SaO_2. Given that $PaCO_2$ did not change significantly between baseline and re-evaluation, it was not surprising to observe that PA-aO_2 increased significantly in the group that developed a ≥3% decrease in SaO_2. Our study shows that the fall in SaO_2 (and in PaO_2) is mainly due to two mechanisms, first a worsening of ventilation-perfusion matching and second a low DL_{CO}. It is not excluded that a decrease in SaO_2 was also due to the opening of a *foramen ovale* in some patients. However, this should only concern very few patients because overall the patients presented hemodynamic improvement at re-evaluation and we did not observe a relationship between the fall in SaO_2 (and in PaO_2) and a worsening of haemodynamic (table 2 and table S6 in the online supplementary material). Our results are reminiscent with a recent study from the ASPIRE Registry dedicated only to patients with idiopathic PAH (7). This study showed that patients with minimal / mild emphysema or with minimal / mild lung fibrosis had a lower DL_{CO} and were associated with a poorer prognosis than those who had no pulmonary parenchymal abnormalities (7). These distinctiveness are similar to our patients with a significant decrease in SaO_2. However, our study included patients with connective tissue disease, 80% of whom had systemic sclerosis that could partly explain the slightly lowered lung volumes and a marked reduced in DL_{CO} in the whole population. Several studies have shown that patients with low DL_{CO} have a poor prognosis despite treatment (7, 22–24). It is difficult to compare our studies with these previous ones because, as we mentioned

previously, our population does not exclusively include patients with idiopathic PAH. From these studies it has been hypothesized that elderly and heavy smokers patients with PAH have significant loss of pulmonary capillaries, which partly explains severe hypoxemia, very low DL_{CO}, pulmonary hypertension and a poor prognosis (23, 25). This has raised controversy, questioning the belonging to group 1 of the clinical classification of pulmonary hypertension of such an elderly population formed mainly of male subjects, smokers or ex-smoker (26). However, destruction of the pulmonary capillary bed must be associated with significant remodelling of the pulmonary arteries to cause severe precapillary pulmonary hypertension (27) as described in the study by Lewis *et al.* (7) as well as in our study. We emphasize on the fact that the diagnostic recommendations of pulmonary hypertension were followed throughout our study and that the attachment or not of these patients with severe pulmonary hypertension and minimal / mild parenchymal abnormalities to group 1 will have to be done at future expert meetings and supported by several clinical studies.

Given the results of our study, measurement of SaO_2 at baseline and at re-evaluation, in room air and at rest could be a non-invasive useful tool in the reassessment of patients with PAH and may be included in risk assessment. The cut-off value of 3% seems accurate to distinguish patients with a poor prognosis. Furthermore, the results of this study allow the identification of factors that were associated with such a decrease in SaO_2. If we compare our study to those that studied the prognostic role of DL_{CO} in PAH (7, 22, 24), it appears less demanding to identify a patient who presents a decrease in SaO_2 on re-evaluation rather than to identify individually a threshold of DL_{CO} to characterize a situation at risk of worsening. However, it is now established that a low DL_{CO} must elicit a high suspicion of a particular form of PAH with a poor prognosis. Indeed, this may correspond to comorbidity, pulmonary veno-occlusive disease, minimal / mild pulmonary emphysema or minimal / mild pulmonary

fibrosis (7, 10, 23). The decrease in SaO_2 and a low DL_{CO} are probably complementary for the evaluation of patients with PAH. In addition, a standardized measurement of SaO_2 by a pulse oximeter is non-invasive and is not very demanding in terms of means.

The main limitation of our study is the retrospective nature of collected data. Some patients were excluded because of missing information (in particular PaO_2 while breathing room air) but there were no differences between included and excluded patients (Online supplementary table S1). Therefore, a selection bias is unlikely. The retrospective nature also implies that we cannot establish a causal link between PAH therapy and the decrease in SaO_2 and even less to identify which drug(s) was or were involved. However, our rationale is based on pathophysiological hypotheses which have been validated (4–6, 28, 29). The other limitation is the absence of a formal assessment of the extent of parenchymal lung lesions on computed tomography of the chest. However, the diagnostic algorithms applied from the start of the study included performing a chest computed tomography which was to be discussed in a multidisciplinary meeting. By including all patients in group 1 of the clinical classification of pulmonary hypertension except congenital heart diseases, our population is heterogeneous. This could also be a limitation. However, a sensitivity analysis showed that most of our results were confirmed when the analysis was performed with only patients with idiopathic, heritable and drug-induced PAH (Online supplementary tables S3 and S4, and figure S2). We did not focus on oxygen therapy as determinant of survival. However, we believe that this could not have introduced a bias because hypoxemia with a PaO_2 <60 mmHg most often appeared between baseline and re-evaluation in two groups with similar mean values at baseline and for most of these patients led to the prescription of oxygen therapy; in an observational study, usually worsening of the disease is likely to predict treatment – not vice versa. Because our data was from a registry, the availability of DL_{CO} and of SaO_2 at baseline

and at re-evaluation led to a multivariate Cox analysis on two different populations, of 579 patients and of 379 patients when DL_{CO} was not and was available, respectively. Therefore, our study does not allow to conclude that the decrease in SaO_2 and DL_{CO} explore the same pathophysiological phenomenon, nor that one is superior to the other in order to predict the course of the disease. Oxyhaemoglobin saturation and DL_{CO} need to be further studied in patients with PAH.

In conclusion, this study shows that a significant decrease in SaO_2 and consequently in PaO_2 is relatively common between diagnosis and first reassessment on PAH therapy. Such a decrease in SaO_2 is linked to poorer outcomes and is observed in a particular subpopulation of patients. Further prospective studies are needed to confirm our data. Our study also suggests that future guidelines should emphasize the value of follow up SaO_2 (and PaO_2) in patients with PAH.

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References

1. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019;53:1801889.

2. Pullamsetti SS, Schermuly R, Ghofrani A, Weissmann N, Grimminger F, Seeger W. Novel and emerging therapies for pulmonary hypertension. *Am J Respir Crit Care Med* 2014;189:394–400.

3. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR, Rabinovitch M. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J* 2019;53:1801887.

4. Dantzker DR, Bower JS. Pulmonary vascular tone improves VA/Q matching in obliterative pulmonary hypertension. *J Appl Physiol Respir Environ Exerc Physiol* 1981;51:607–613.

5. Agustí AG, Rodriguez-Roisin R. Effect of pulmonary hypertension on gas exchange. *Eur Respir J* 1993;6:1371–1377.

6. Bratel T, Lagerstrand L, Brodin L-A, Nowak J, Randmaa I. Ventilation-perfusion relationships in pulmonary arterial hypertension: effect of intravenous and inhaled prostacyclin treatment. *Respir Physiol Neurobiol* 2007;158:59–69.

7. Lewis RA, Thompson AAR, Billings CG, Charalampopoulos A, Elliot CA, Hamilton N, Hill C, Hurdman J, Rajaram S, Sabroe I, Swift AJ, Kiely DG, Condliffe R. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2020;55:2000041.

8. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107:216–223.

9. Hoeper MM, Pletz MW, Golpon H, Welte T. Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2007;29:944–950.

10. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015;46:903–975.

11. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.

12. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. *J Appl Physiol Respir Environ Exerc Physiol* 1979;46:599–602.

13. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, Chaouat A, Chabanne C, Bourdin A, Parent F, Montani D, Simonneau G, Humbert M, Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017;50:170089.

14. Rota M, Antolini L, Valsecchi MG. Optimal cut-point definition in biomarkers: the case of censored failure time outcome. *BMC Med Res Methodol* 2015;15:24.

15. Lacasse Y, Tan A-YM, Maltais F, Krishnan JA. Home Oxygen in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2018;197:1254–1264.

16. West JB. Physiological Effects of Chronic Hypoxia. *N Engl J Med* 2017;376:1965–1971.

17. Collins J-A, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. *Breathe (Sheff)* 2015;11:194–201.

18. Smith KA, Yuan JX-J. Hypoxia-inducible factor-1α in pulmonary arterial smooth muscle cells and hypoxia-induced pulmonary hypertension. *Am J Respir Crit Care Med* 2014;189:245–246.

19. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43:5S-12S.

20. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376–387.

21. Ling Y, Johnson MK, Kiely DG, Condliffe R, Elliot CA, Gibbs JSR, Howard LS, Pepke-Zaba J, Sheares KKK, Corris PA, Fisher AJ, Lordan JL, Gaine S, Coghlan JG, Wort SJ, Gatzoulis MA, Peacock AJ. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care Med* 2012;186:790–796.

22. Trip P, Nossent EJ, de Man FS, van den Berk IAH, Boonstra A, Groepenhoff H, Leter EM, Westerhof N, Grünberg K, Bogaard H-J, Vonk-Noordegraaf A. Severely reduced

diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. *Eur Respir J* 2013;42:1575–1585.

23. Olsson K, Fuge J, Meyer K, Welte T, Hoeper M. More on idiopathic pulmonary arterial hypertension with a low diffusing capacity. *Eur Respir J* 2017;50:1700354.

24. Hoeper MM, Pausch C, Grünig E, Klose H, Staehler G, Huscher D, Pittrow D, Olsson KM, Vizza CD, Gall H, Benjamin N, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Rosenkranz S, Ewert R, Kaemmerer H, Lange TJ, Kabitz H-J, Skowasch D, Skride A, Jureviciene E, Paleviciute E, Miliauskas S, Claussen M, Behr J, Milger K, *et al.* Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. *J Heart Lung Transplant* 2020;39:1435–1444.

25. Hoeper M, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? *Lancet Respir Med* 2017;5:676–678.

26. Godinas L, Harari S, Barberà JA, Montani D. Mild parenchymal lung disease is still lung disease. *Eur Respir J* 2020;56:.

27. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med* 2002;166:314–322.

28. Dantzker DR, D'Alonzo GE, Bower JS, Popat K, Crevey BJ. Pulmonary gas exchange during exercise in patients with chronic obliterative pulmonary hypertension. *Am Rev Respir Dis* 1984;130:412–416.

29. Weatherald J, Farina S, Bruno N, Laveneziana P. Cardiopulmonary Exercise Testing in Pulmonary Hypertension. *Ann Am Thorac Soc* 2017;14:S84–S92.

Figure legends

Figure 1: Flowchart of study population.

Among the 3483 patients, 719 were included in the main analysis.

6MWD: six-minute walk distance; ABG: arterial blood gases; BNP: brain natriuretic peptide; CHD: congenital heart disease; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAH: pulmonary arterial hypertension; PCH: pulmonary capillary haemangiomatosis; PaO_2: partial pressure of oxygen in arterial blood; PVOD: pulmonary veno-occlusive disease; RAP: right atrial pressure, WHO/NYHA: world health organization/New York Heart Association functional class

Figure 2: Comparison of transplantation-free survival in patients with a ≥3% decrease in SaO_2 and patients with no or less than 3% of decrease in SaO_2. Number of patients left at risk at 0, 2, 4 and 6 years in the two groups.

SaO_2: saturation of oxygen in arterial blood

Figure 1

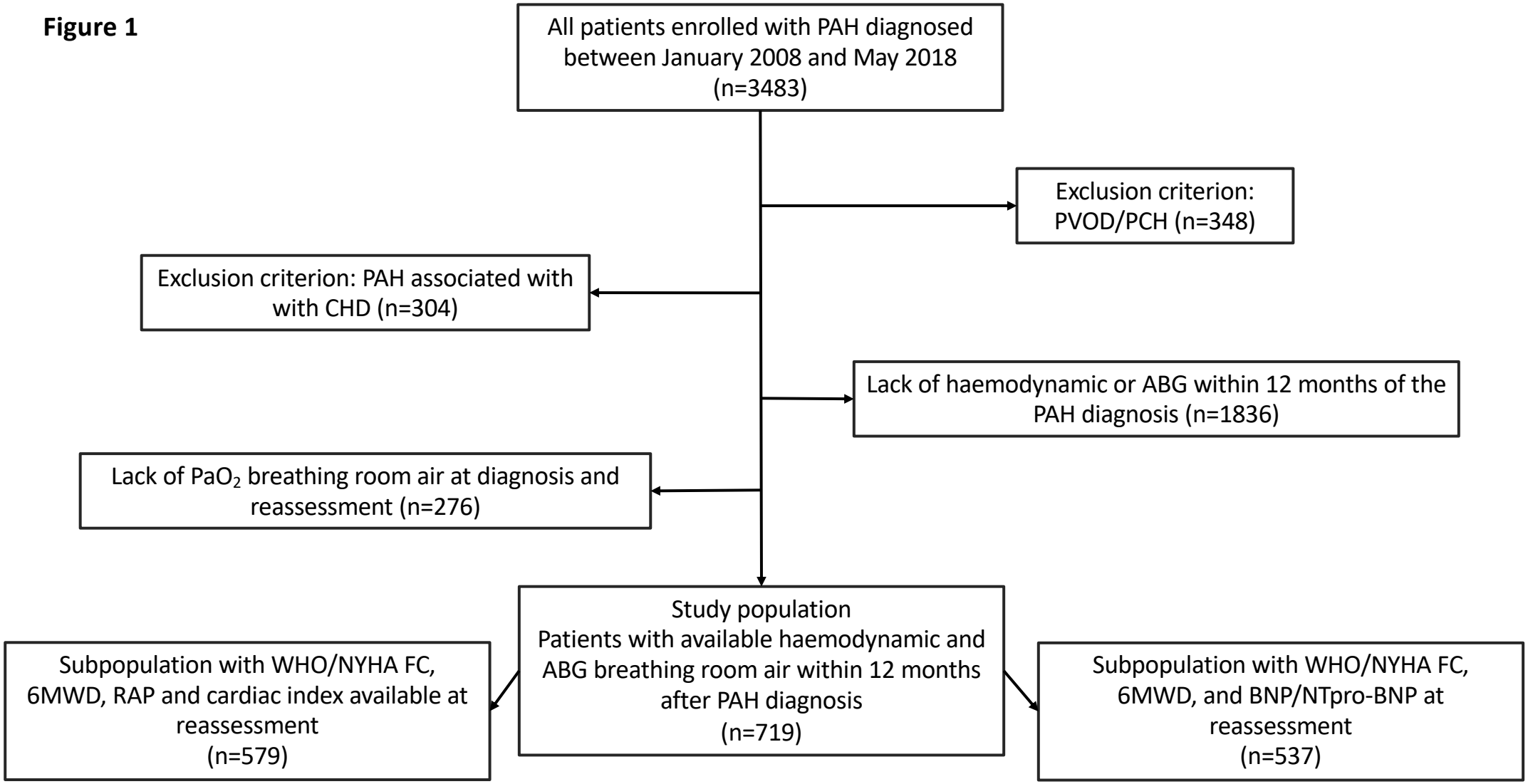
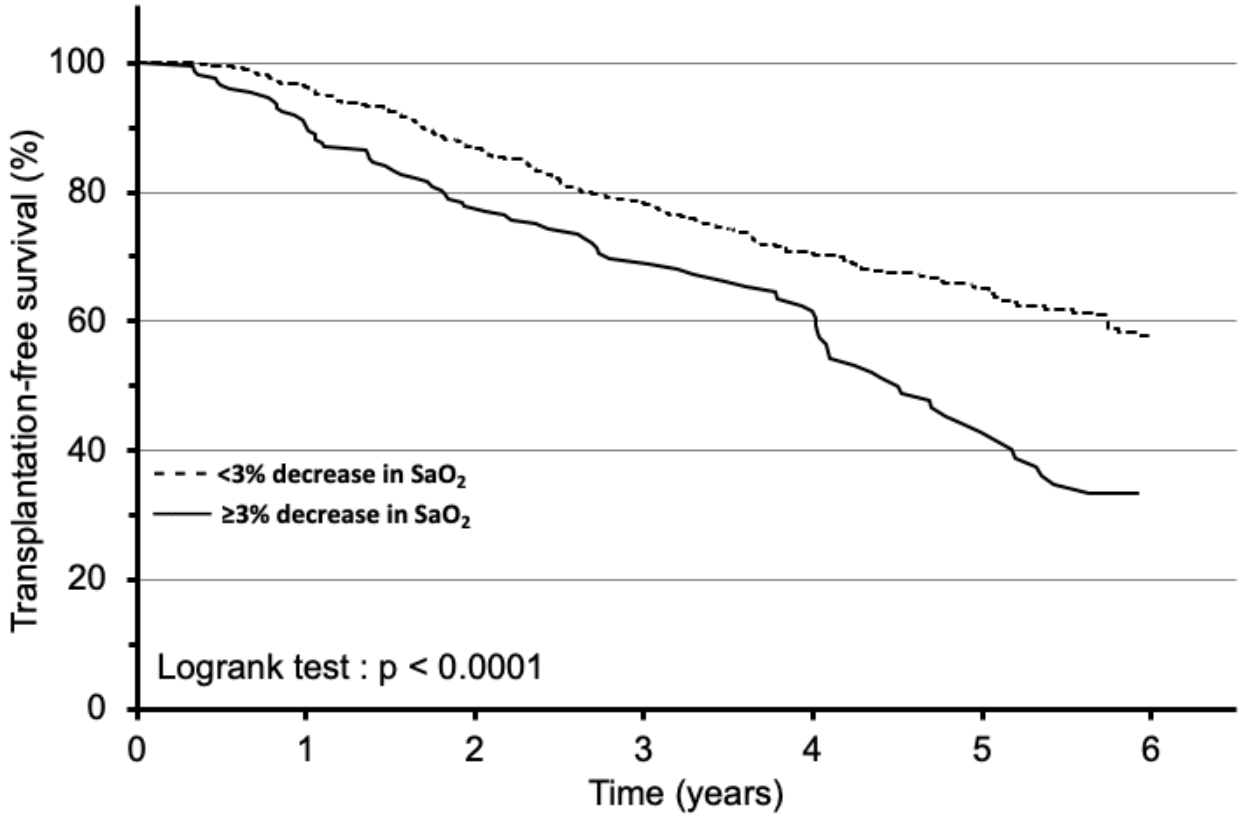

All patients enrolled with PAH diagnosed between January 2008 and May 2018 (n=3483)
Exclusion criterion: PVOD/PCH (n=348)
Exclusion criterion: PAH associated with with CHD (n=304)
Lack of haemodynamic or ABG within 12 months of the PAH diagnosis (n=1836)
Lack of PaO_2 breathing room air at diagnosis and reassessment (n=276)
Study population
Patients with available haemodynamic and ABG breathing room air within 12 months after PAH diagnosis
(n=719)
Subpopulation with WHO/NYHA FC, 6MWD, RAP and cardiac index available at reassessment
(n=579)
Subpopulation with WHO/NYHA FC, 6MWD, and BNP/NTpro-BNP at reassessment
(n=537)

Figure 2



Survival rate according to SaO_2 change at re-evaluation:
Patients left at risk (transplantation-free survival rate)

≥3% decrease in SaO_2	173 (100%)	120 (78%)	61 (61%)	19 (33%)
<3% decrease in SaO_2	546 (100%)	415 (87%)	219 (71%)	196 (58%)

Table 1: Comparison of demographic, PAH diagnosis, functional, biologic test and hemodynamic data at baseline in patients with a ≥3% decrease in SaO_2 and in patients with a < 3% decrease in SaO_2 at re-evaluation

	≥3% decrease in SaO_2 (N=173)			<3% decrease in SaO_2 (N=546)			p	All (N=719)
Demographic data								
Age, years		64	(12)		58	(15)	<0.0001	60 (14)
Female sex, n (%)		98	(57)		312	(57)	0.91	410 (57%)
BMI, kg/m^2		27.4	(6.4)		27.3	(6.6)	0.87	27.4 (6.6)
Smoker or ex-smoker, n (%)	n=167	98	(59)	n=524	297	(57)	0.65	395 (57)
Smoking history, pack-years	n=80	31	(18)	n=245	34	(21)	0.42	33 (20)
Comorbidities								
Systemic hypertension, n (%)		87	(50)		251	(46)	0.44	338 (47)
CAD, n (%)		22	(13)		65	(12)	0.95	87 (12)
Diabetes Mellitus, n (%)		61	(35)		136	(25)	0.046	197 (27)
Obesity, n (%)		45	(26)		150	(27)	0.81	195 (27)
PAH diagnosis*								
Idiopathic, n (%)		76	(44)		204	(37)	0.12	280 (39)
Heritable, n (%)		1	(1)		33	(6)	0.003	34 (<1)
Drug-induced, n (%)		15	(9)		55	(10)	0.59	70 (10)
Associated with CTD, n (%)		57	(33)		125	(23)	0.008	182 (25)
Associated with portal hypertension, n (%)		21	(12)		117	(21)	0.007	138 (19)
Associated with HIV infection, n (%)		3	(2)		12	(2)	0.71	15 (<1)
Functional parameters								
NYHA functional class, n (%)								
I or II		44	(26)		159	(29)		203 (28)
III		107	(62)		323	(59)	0.65	430 (60)
IV		21	(12)		62	(11)		83 (12)
Six-minute-walk distance, m	n=149	272	(147)	n= 145	314	(151)	0.005	303 (151)
FVC, % pred	n= 153	89	(21)	n=460	94	(20)	0.017	92 (21)
FEV_1, % pred	n= 159	82	(19)	n=482	86	(19)	0.009	85 (19)
DL_{CO}, % pred	n= 128	42	(17)	n=408	51	(20)	<0.0001	49 (20)
PaO_2 on room air, mm Hg	n= 173	68	(14)	n=546	65	(17)	0.058	66 (16)
$PaCO_2$ on room air, mm Hg	n = 173	34	(6)	n=546	34	(7)	0.41	34 (7)

SaO_2 on room air, %	n= 173	92	(5)	n=546	90	(8)	0.049	90 (8)
$P_{A-a}O_2$, mmHg	n= 172	40	(14)	n=536	43	(17)	0.064	42 (16)
Laboratory data								
NT-proBNP, ng/L	n=61	1955	(2514)	n=177	2075	(3281)	0.80	2045 (3098)
BNP, ng/L	n=93	494	(686)	n=318	423	(1519)	0.088	439 (1375)
Hemoglobin, g/dL	n=121	14.3	(2.1)	n=385	14.4	(2.3)	0.64	14.3 (2.3)
Haemodynamic								
mPAP, mm Hg	n=173	44	(9)	n=546	47	(12)	0.033	46 (12)
RAP, mm Hg	n=157	8	(5)	n=512	9	(5)	0.99	9 (5)
PAWP, mm Hg	n=162	9	(4)	n=529	9	(4)	0.88	9 (4)
CO, L/min	n=167	4.4	(1.3)	n=538	4.7	(1.7)	0.22	4.6 (1.6)
CI, L/min/m^2	n=166	2.5	(0.7)	n=535	2.6	(0.9)	0.16	2.6 (0.8)
PVR, WU	n=156	8.8	(4.4)	n=522	9.2	(4.9)	0.34	9.1 (4.7)
SvO_2, (%)	n=88	61	(11)	n=313	63	(10)	0.076	63 (10)

Values are expressed as the mean (SD) or as number and frequency.

*N: population size; n: available data. * Fisher's exact test*

BMI: body mass index; BNP: brain natriuretic peptide; CAD: coronary artery disease; CI: cardiac index; CO: cardiac output; CTD: connective tissue disease; $P_{A-a}O_2$: alveolo-arterial difference in oxygen; DL_{CO}: diffusing capacity for carbon monoxide corrected for haemoglobin level; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HIV: human immunodeficiency virus; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York heart association; PAH: pulmonary arterial hypertension; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure, SaO_2: saturation of oxygen in arterial blood; SvO_2: saturation of oxygen in venous blood.

Table 2: Change in characteristics of patients with a ≥ 3% decrease in SaO_2 and patients with a < 3% decrease in SaO_2

	≥3% decrease in SaO_2 (N=173)			<3% decrease in SaO_2 (N=546)			p
Functional parameters							
NYHA functional class, n (%)							
Improved	n=171	61	(36)	n=544	245	(45)	0.031
Unchanged or impaired		110	(64)		299	(55)	
Six-minute-walk distance, m	n=122	27	(103)	n=428	51	(120)	0.046
FVC, % pred	n=105	0	(15)	n=326	3	(12)	0.005
FEV_1, % pred	n=106	-2	(11)	n=344	2	(11)	0.0001
DL_{CO}, % pred	n=76	-3	(9)	n=276	0	(10)	0.013
PaO_2 on room air, mm Hg	n=173	-17	(12)	n=546	6	(17)	<0.0001
$PaCO_2$ on room air, mm Hg	n=171	1.3	(5.0)	n=531	0.4	(6.3)	0.15
SaO_2 on room air, %	n=173	-9	(7)	n=546	3	(6)	NA
$P_{A\text{-}a}O_2$, mmHg	n=170	16	(12)	n=522	-6	(14)	<0.0001
Laboratory data							
NT-proBNP, ng/L	n=49	-616	(2028)	n=154	-947	(2300)	0.013
BNP, ng/L	n=76	-187	(526)	n=276	-184	(377)	0.15
Hemoglobin, g/dL	n=113	-1	(2)	n=367	-1	(2)	0.82
Haemodynamic							
mPAP, mm Hg	n=173	-4	(10)	n=546	-7	(11)	0.001
RAP, mm Hg	n=120	0	(5)	n=392	-1	(5)	0.049
PAWP, mm Hg	n=159	1	(4)	n=516	1	(5)	0.10
CO, L/min	n=162	1.0	(1.5)	n=527	1.2	(1.7)	0.21
CI, L/min/m^2	n=160	0.5	(0.9)	n=516	0.6	(0.9)	0.26
PVR, WU	n=149	-3	(5)	n=501	-4	(4)	0.13
SvO_2, (%)	n=71	5	(11)	n=259	5	(8)	0.25

Values are expressed as the mean (SD) or as number and frequency.

N: population size; n: available data.

BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; $P_{A\text{-}a}O_2$: alveolo-arterial difference in oxygen; DL_{CO}: diffusing capacity for carbon monoxide corrected for haemoglobin level; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York heart association; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PAWP: pulmonary arterial wedge pressure ; PVR: pulmonary vascular resistance; RAP: right atrial pressure, SaO_2: saturation of oxygen in arterial blood; SvO_2: saturation of oxygen in venous blood.

Table 3: Univariate Cox regression analysis of risk factors and transplantation-free survival.

	Events / Available obs.	Hazard ratio (95% CI)	p
Baseline characteristics			
Age ≥ 60 at baseline, yes	261 / 719	2.24 (1.73-2.91)	<0.0001
Male sex, yes	261 / 719	1.25 (0.98-1.59)	0.077
PAH associated with CTD, yes	261 / 719	1.62 (1.25 - 2.11)	0.0003
Baseline SaO_2 (per 5% dec.)	261 / 719	1.14 (1.06 - 1.21)	0.0001
Change from baseline at first re-evaluation			
≥ 3% decrease in SaO_2, yes	261 / 719	1.81 (1.43-2.34)	<0.0001
Functional data at first re-evaluation			
FVC (per 10% dec.)	177 / 488	1.11 (1.04 - 1.19)	0.002
FEV_1 (per 10% dec.)	178 / 495	1.12 (1.04 - 1.21)	0.004
DL_{CO} (per 10% dec.)	147 / 431	1.42 (1.29 - 1.56)	< 0.0001
PaO_2 (per 10 mmHg dec.)	261 / 719	1.29 (1.20 - 1.40)	< 0.0001
$PaCO_2$ (per 10 mmHg dec.)	256 / 708	1.14 (0.90 - 1.43)	0.28
Haemodynamic at first re-evaluation			
mPAP (per 10 mmHg inc.)	260 / 717	1.20 (1.08 - 1.32)	0.0005
PVR (per 10 WU inc.)	244 / 685	2.17 (1.56 - 3.03)	< 0.0001
SVi (per 10 ml/min/m² dec.)	182 / 499	1.36 (1.18 - 1.57)	< 0.0001
SvO_2 (per 10% dec.)	130 / 420	1.71 (1.39 - 2.11)	< 0.0001
ESC/ERS Risk at first re-evaluation			
WHO/NYHA III-IV vs. I-II	261 / 718	2.36 (1.85 - 3.01)	< 0.0001
6MWD ≤ 440 m, yes	213 / 622	3.67 (2.44 - 5.50)	< 0.0001
RAP ≥ 8 mmHg, yes	247 / 690	1.91 (1.48 - 2.45)	< 0.0001
CI < 2.5 l/min/m², yes	244 / 687	2.06 (1.57 - 2.69)	< 0.0001
BNP ≥ 50 ng/ml or NT-proBNP ≥300, yes	234 / 648	2.50 (1.86 - 3.35)	< 0.0001
High-risk of death or transplantation			
Intermediate or high risk (a), yes	193 / 579	3.72 (2.63 - 5.26)	< 0.0001
Intermediate or high risk (b), yes	178 / 537	3.15 (2.22 - 4.46)	< 0.0001

Events: transplantation-free survival; available obs: available observations; inc.: increment; dec.: decrement.

§*: at first re-evaluation*

(a): New York heart association functional class I or II; six-minute-walk distance > 440m; right atrial pressure < 8 mmHg; cardiac index ≥ 2.5 l/min/m^2. Patients with less than 3 of these criteria were in the intermediate and high-risk groups at first re-evaluation.

(b): New York heart association functional class I or II; six-minute-walk distance > 440m; brain natriuretic peptide < 50 ng/L or N-terminal prohormone of brain natriuretic peptide < 300 ng/L. Patients with less than 2 of these criteria were in the intermediate and high-risk groups at first re-evaluation.

CI: cardiac index; CTD: connective tissue disorder; DL_{CO}: diffusing capacity for carbon monoxide corrected for haemoglobin level; *FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure NYHA: New York heart association; $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PAH: pulmonary arterial hypertension; PaO_2: partial pressure of oxygen in arterial blood; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SaO_2: saturation of oxygen in arterial blood, SVi: stroke volume index; SvO_2: saturation of oxygen in venous blood; 6MWD: six-meter-walk distance*

Table 4: Multivariate Cox regression analyses*.

	Events / Patients	Hazard ratio (95% CI)	p
Baseline SaO_2, RCS		NA	0.0005
≥ 3% decrease in SaO_2, yes		1.54 (1.13 - 2.10)	0.007
PAH associated with CTD, yes		1.60 (1.18 - 2.16)	0.002
WHO/NYHA III-IV vs. I-II[§]	210 / 579	1.52 (1.15 - 2.02)	0.004
6MWD ≤ 440 m, yes[§]		2.22 (1.46 - 3.37)	0.0002
RAP ≥ 8 mmHg, **yes**[§]		1.54 (1.17 - 2.04)	0.002
CI < 2.5 l/min/m², **yes**[§]		1.68 (1.24 - 2.26)	0.0007

	Events / Patients	Hazard ratio (95% CI)	p
Baseline SaO_2, RCS		NA	0.0002
≥ 3% decrease in SaO_2, yes	210 / 579	1.54 (1.13 - 2.10)	0.007
PAH associated with CTD, yes		1.57 (1.16 - 2.13)	0.004
Intermediate or high risk[#]**, yes**		2.61 (1.86 - 3.64)	<0.0001

6MWD: six-minute walk distance; CI: cardiac index; CTD: connective tissue disorder; NYHA: New York heart association; PAH: pulmonary arterial hypertension, RAP: right atrial pressure, SaO_2: saturation of oxygen in arterial blood; RCS: Restricted Cubic Spline transform; NA: not available.

**: Multivariate Cox analysis excluding diffusing capacity of the lungs for carbon monoxide.*

[§]*: at first re-evaluation*

[#]*: New York heart association functional class I or II; six-minute-walk distance > 440m; right atrial pressure < 8 mmHg; cardiac index ≥ 2.5 l/min/m². Patients with less than 3 of these criteria were in the intermediate and high-risk groups at first re-evaluation.*

Online Supplementary material

Outcomes of patients with decreased arterial oxyhaemoglobin saturation on pulmonary arterial hypertension drugs

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Methods

The institutional review board of *CHRU de Nancy* also approved this study on March 11, 2020 (referral N° 260). In accordance with French regulations, informed consent was waived due to the retrospective nature of the present study.

The following data are entered in the French Registry: morphometric data, type of pulmonary hypertension regularly adapted to the current clinical classification [1], WHO/NYHA functional class, 6-minute walk distance, brain natriuretic peptide (BNP) or N-terminal prohormone brain natriuretic peptide (NTpro-BNP), and complete hemodynamic results. The Registry also provides percentage of predicted values of forced vital capacity, (forced expiratory volume in one second) FEV_1 and diffusing capacity of the lungs for carbon monoxide (DL_{CO}). Investigators were instructed to include all new cases of PAH immediately after performing the right heart catheterization which confirmed the diagnosis and by individually verifying in a multidisciplinary meeting that each of the patients verified the current PAH diagnostic algorithm at the time of inclusion in the French registry, the latter being that of the 2015 ESC/ERS guidelines.

In a previous study of 90 PAH patients, seen at Nancy University Hospital, France, having had pulse oxygen saturation (SpO_2) in room air at diagnosis and at first re-evaluation under PAH treatment, we found that 29 (32%) presented at first re-evaluation a decrease $\geq$ 3% in SpO_2 (Chaouat *et al*, unpublished observation). From this previous study, the cut-point of a decrease $\geq$ 3% in arterial oxyhaemoglobin saturation (SaO_2) was empirically determined (see figure E1 in the online data supplement).

The ESC/ERS guidelines risk stratification table was used according to the French Registry invasive and non-invasive approaches, as previously described [2, 3]. Low risk patients were those who presented at re-evaluation three or four of the following criteria: 1) WHO/NYHA

functional class I or II, 2) 6-minute walk distance (6MWD) > 440 m, 3) right atrial pressure (RAP) < 8 mmHg and 4) cardiac index ≥ 2.5 L/min/m2. Noninvasively, low risk patients were those who presented with two or three of the following criteria at re-evaluation: 1) WHO/NYHA functional class I or II, 2) 6MWD >440 m, 3) BNP < 50 ng/L or NT-proBNP < 300 ng/L.

Statistical analysis

Both analyses were performed in 2 steps: a first univariate selection step identifying relevant parameters according to their clinical interest, availability (less than 5% missing values) and significance ($p < 0.05$). When not binary, the continuous parameters were split according to the same methods described above or recognized diagnosis criteria before entering a multivariable analysis. The final model retained only the remaining significant covariables after interactive backward selection. The validity conditions of the models were thoroughly checked: absence of correlation or interaction and goodness-of-fit.

References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* 2019; 53: 1801913.
2. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Respir. J.* 2015; 46: 903–975.
3. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, Chaouat A, Chabanne C, Bourdin A, Parent F, Montani D, Simonneau G, Humbert M, Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur. Respir. J.* 2017; 50: 170089.

Results

Table S1: Comparison of patients included and those excluded from the study

Features	Included patients (N=719)		Excluded patients (N=2764)		p
Demographic data					
Age, years	60	(14)	60	(15)	0.35
Female, n (%)	410	(57)	1664	(60)	0.12
I, h, d PAH, n (%)	384.	(53)	1354	(49)	0.005
Other groups PAH, n (%)	335	(47)	1410	(51)	
Functional parameters					
WHO/NYHA functional class, n (%)					
- I or II	203	(28)	877	(32)	0.071
- III	430	(60)	1511	(55)	-
- IV	83	(12)	337	(12)	-
Six-minute walk distance, m	304	(151)	300	(148)	0.67
Haemodynamic					
mPAP, mmHg	46	(12)	45	(12)	0.008
CI, L/min/m^2	2.6	(0.8)	2.6	(0.8)	0.009
PVR, WU	9.10	(4.74)	8.63	(4.93)	0.001

Values are expressed as the mean (SD) or as number and frequency.

N: population size.

CI: cardiac index; i, h, d: idiopathic, heritable, drug-induced; mPAP: mean pulmonary artery pressure; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; WHO/NYHA: world health organization/New York heart association functional class

Table S2: Risk stratification between patients with a ≥3% decrease in SaO_2 and patients with a < 3% decrease in SaO_2 at re-evaluation

		≥3% decrease in SaO_2			<3% decrease in SaO_2		p
Low-risk status [(a)]							
≥ 3	n=119	31	(26%)	n=460	218	(47%)	<0.0001
Low-risk status [(b)]							
≥ 2	n=110	31	(28%)	n=427	191	(45%)	0.002

n: available data.

(a) Criteria: New York heart association functional class I or II; six-minute walk distance > 440m; right atrial pressure < 8 mmHg; cardiac index > 2.5 l/min/m^2 at first re-evaluation.

(b) Criteria: New York heart association functional class I or II; six-minute walk distance > 440m; brain natriuretic peptide < 50 pg/ml or N-terminal prohormone of brain natriuretic peptide < 300 pg/ml at first re-evaluation.

Table S3: Univariate Cox regression analysis of transplantation-free survival limited to the population of patients with idiopathic, heritable or drug-induced PAH.

	Events / Available obs.	Hazard ratio (95% CI)	p
Baseline characteristics			
Age ≥ 60 at baseline, yes	117 / 394	3.63 (2.36 - 5.58)	< 0.0001
Male sex, yes	117 / 394	1.57 (1.09 - 2.26)	0.015
PAH associated with CTD, yes	117 / 394	3.40 (1.07 - 10.8)	0.037
Baseline SaO_2 (per 5% dec.)	117 / 394	1.11 (1.02 - 1.22)	0.017
Change from baseline at first re-evaluation			
≥ 3% decrease in SaO_2, yes	117 / 394	2.36 (1.62 - 3.43)	< 0.0001
Functional data at first re-evaluation			
FVC (per 10% dec.)	76 / 264	1.13 (1.01 - 1.25)	0.033
FEV_1 (per 10% dec.)	77 / 267	1.15 (1.02 - 1.30)	0.024
DL_{CO} (per 10% dec.)	60 / 225	1.61 (1.39 - 1.85)	< 0.0001
PaO_2 (per 10 mmHg dec.)	117 / 394	1.41 (1.25 - 1.59)	< 0.0001
$PaCO_2$ (per 10 mmHg dec.)	114 / 387	1.40 (0.98 - 2.01)	0.065
Haemodynamic at first re-evaluation			
mPAP (per 10 mmHg inc.)	117 / 393	1.25 (1.09 - 1.45)	0.002
PVR (per 10 WU inc.)	110 / 377	2.26 (1.42 - 3.60)	0.0005
SVi (per 10 ml/min/m² dec.)	71 / 265	1.47 (1.16 - 1.86)	0.001
SvO_2 (per 10% dec.)	47 / 228	2.01 (1.45 - 2.80)	< 0.0001
ESC/ERS Risk at first re-evaluation			
WHO/NYHA III-IV vs. I-II	117 / 394	3.13 (2.16 - 4.55)	< 0.0001
6MWD ≤ 440 m, yes	103 / 358	7.29 (3.53 - 15.0)	< 0.0001
RAP ≥ 8 mmHg, yes	110 / 376	2.34 (1.60 - 3.42)	< 0.0001
CI < 2.5 l/min/m², yes	108 / 377	1.96 (1.32 - 2.91)	0.0008
BNP ≥ 50 ng/ml or NT-proBNP ≥300, yes	107 / 360	4.97 (2.92 - 8.47)	< 0.0001
High-risk of death or transplantation			
Intermediate or high risk (a), yes	91 / 330	5.31 (3.05 - 9.26)	< 0.0001
Intermediate or high risk (b), yes	85 / 307	6.65 (3.52 - 12.6)	< 0.0001

Events: transplantation-free survival; available obs: available observations; inc.: increment; dec.: decrement.

(a): New York heart association functional class I or II; six-minute-walk distance > 440m; right atrial pressure < 8 mmHg; cardiac index ≥ 2.5 l/min/m^2. Patients with less than 3 of these criteria were in the intermediate and high-risk groups at first re-evaluation.

(b): New York heart association functional class I or II; six-minute-walk distance > 440m; brain natriuretic peptide < 50 ng/L or N-terminal prohormone of brain natriuretic peptide < 300 ng/L. Patients with less than 2 of these criteria were in the intermediate and high-risk groups at first re-evaluation.

BNP: Brain natriuretic peptide; CI: cardiac index; CTD: connective tissue disorder; DL_{CO}: diffusing capacity for carbon monoxide corrected for haemoglobin level; *FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure NYHA: New York heart association; $PaCO_2$: partial pressure of carbon dioxide in arterial blood, PAH: pulmonary arterial hypertension; PaO_2: partial pressure of oxygen in arterial blood; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SaO_2: saturation of oxygen in arterial blood, SVi: stroke volume index; SvO_2: saturation of oxygen in venous blood; 6MWD: six-meter-walk distance*

Table S4: Multivariate Cox regression analysis of transplantation-free survival limited to the population of patients with idiopathic, heritable or drug-induced PAH.

	Events / Patients	Hazard ratio (95% CI)	p
Baseline SaO_2, RCS	103 / 330	NA	0.0002
≥ 3% decrease in SaO_2, yes		2.09 (1.35 - 3.22)	0.0009
WHO/NYHA III-IV vs. I-II[§]		1.85 (1.23 - 2.79)	0.003
6MWD ≤ 440 m, yes[§]		2.41 (1.27 - 4.58)	0.007
RAP ≥ 8 mmHg, **yes**[§]		1.56 (1.04 - 2.33)	0.031
CI < 2.5 l/min/m², **yes**[§]		1.74 (1.14 - 2.66)	0.010

	Events / Patients	Hazard ratio (95% CI)	p
Baseline SaO_2, RCS	103 / 330	NA	0.029
≥ 3% decrease in SaO_2, yes		1.97 (1.27 - 3.04)	0.002
Intermediate or high risk[#], yes		2.44 (1.49 - 3.99)	0.0004

Events: transplantation-free survival.

[§]*: at first re-evaluation*

CI: cardiac index; NYHA: New York heart association; RAP: right atrial pressure; RCS: Restricted Cubic Spline transform; NA: not available; SaO_2: saturation of oxygen in arterial blood; 6MWD: six-meter-walk distance.

[#]*: New York heart association functional class I or II; six-minute-walk distance > 440m; right atrial pressure < 8 mmHg; cardiac index ≥ 2.5 l/min/m^2. Patients with less than 3 of these criteria were in the intermediate and high-risk groups at first re-evaluation.*

Table S5: Multivariate Cox regression analysis with diffusing capacity of the lungs for carbon monoxide as a covariate

	Events / Patients	Hazard ratio (95% CI)	p
≥ 3% decrease in SaO_2, yes		1.26 (0.84 - 1.90)	0.26
Age ≥ 60 years, yes		0.95 (0.64 - 1.42)	0.82
Male sex, yes		1.16 (0.81 - 1.65)	0.43
PAH associated with CTD, yes		1.49 (1.05 - 2.12)	0.028
DL_{CO} < 50% pred., yes	133 / 379	1.82 (1.21 - 2.74)	0.004
WHO/NYHA, III-IV vs. I-II[§]		1.62 (1.13 - 2.33)	0.009
6MWD ≤ 440 m, yes[§]		2.28 (1.33 - 3.90)	0.003
RAP ≥ 8 mmHg, yes[§]		1.37 (0.97 - 1.95)	0.077
CI < 2.5 l/min/m², yes[§]		1.66 (1.12 - 2.47)	0.011

6MWD: six-minute walk distance; CI: cardiac index; CTD: connective tissue disorder; DL_{CO}: diffusing capacity of the lungs for carbon monoxide; WHO/NYHA: world health organization/New York heart association functional class; PAH: pulmonary arterial hypertension, RAP: right atrial pressure, SaO_2: saturation of oxygen in arterial blood

[§]*: at first re-evaluation*

Table S6: Correlations between the change in SaO_2 and the change in PaO_2 between the baseline (V0) and reassessment (V1) and various variables.

		$SaO_{2\ V1}$ - $SaO_{2\ V0}$	$PaO_{2\ V1}$- $PaO_{2\ V0}$
$PaCO_{2\ V1}$- $PaCO_{2\ V0}$	r	-0.12	-0,13
	p	0.002	0,0007
	n	702	702
$DL_{CO\ V1}$- $DL_{CO\ V0}$	r	0.16	0,16
	p	0.002	0,003
	n	352	352
RAP_{V1}- RAP_{V0}	r	-0.13	-0.13
	p	0.004	0.004
	n	512	512
CI_{V1}- CI_{V0}	r	0.08	0,07
	p	0.044	0,071
	n	676	676
PVR_{V1}-PVR_{V0}	r	-0.096	-0.11
	p	0.014	0.005
	n	650	640
$SvO_{2\ V1}$- $SvO_{2\ V0}$	r	0.10	0,11
	p	0.078	0,037
	n	330	330

CI: cardiac index; DL_{CO}: diffusing capacity for carbon monoxide; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PVR: pulmonary vascular

resistance; RAP: right atrial pressureSaO_2: saturation of oxygen in arterial blood; SvO_2: saturation of oxygen in venous blood

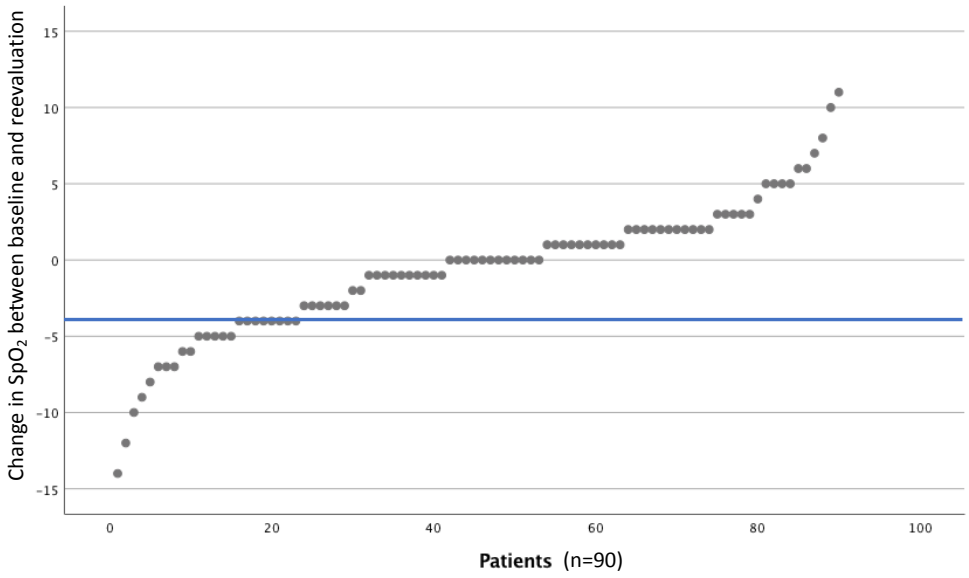
Table S7: Two models of multivariate logistic regression with a 3% or more decrease in SaO_2 between baseline and reassessment as dependent variable.

	Events / Patients	Odd ratio (95% CI)	p
Age (per 10 years inc.)		1.09 (0.91 - 1.29)	0.36
PAH associated with CTD, yes		1.13 (0.72 - 1.78)	0.60
DL_{CO} (per 10% dec.)	107/454	1.28 (1.12 - 1.47)	0.0004
6MWD (per 100m dec.)		1.11 (0.93 – 1.33)	0.25
RAP (per 1mmHg inc.)		1.01 (0.96 – 1.06)	0.67

	Events / Patients	Odd ratio (95% CI)	p
Age ≥ 60 years, yes		1.27 (0.78 - 2.08)	0.33
PAH associated with CTD, yes		1.23 (0.78 - 1.93)	0.38
DL_{CO} < 50% pred., yes	107/454	2.33 (1.39 - 3.91)	0.001
6MWD ≤ 440 m, yes		0.99 (0.52 – 1.89)	0.99
RAP ≥ 8 mmHg, yes		1.16 (0.74 – 1.82)	0.51

6MWD: six-minute walk distance; CTD: connective tissue disorder; DL_{CO}: diffusing capacity of the lungs for carbon monoxide; PAH: pulmonary arterial hypertension, RAP: right atrial pressure

Figure S1: Chaouat *et al*, unpublished observation, the cut-point of a decrease ≥ 3% in SpO_2 was empirically determined



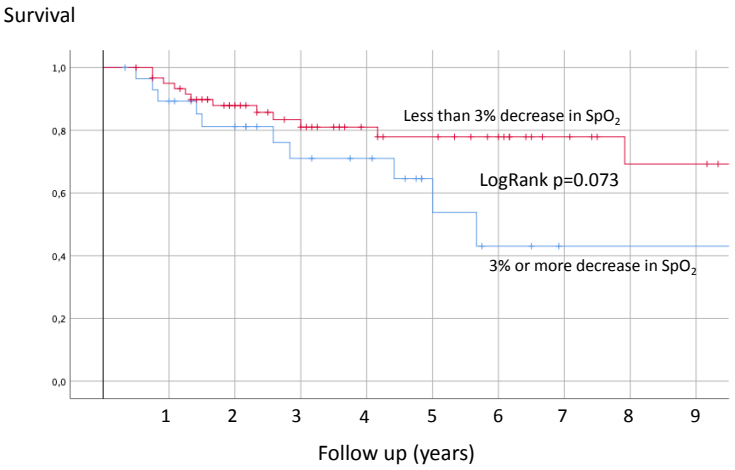


Figure S2: Transplantation-free survival sensitivity analyses

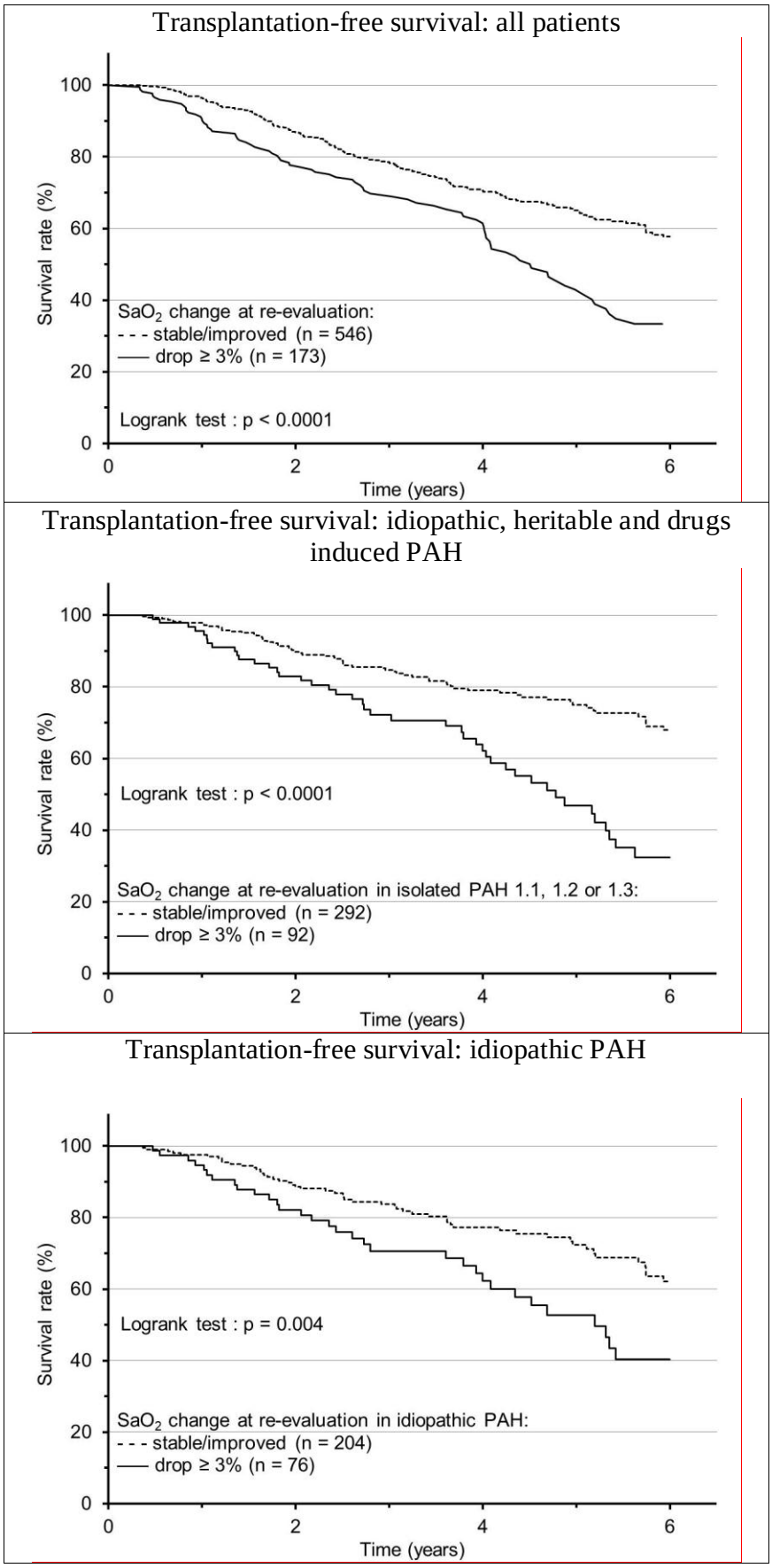


Figure S2 continued

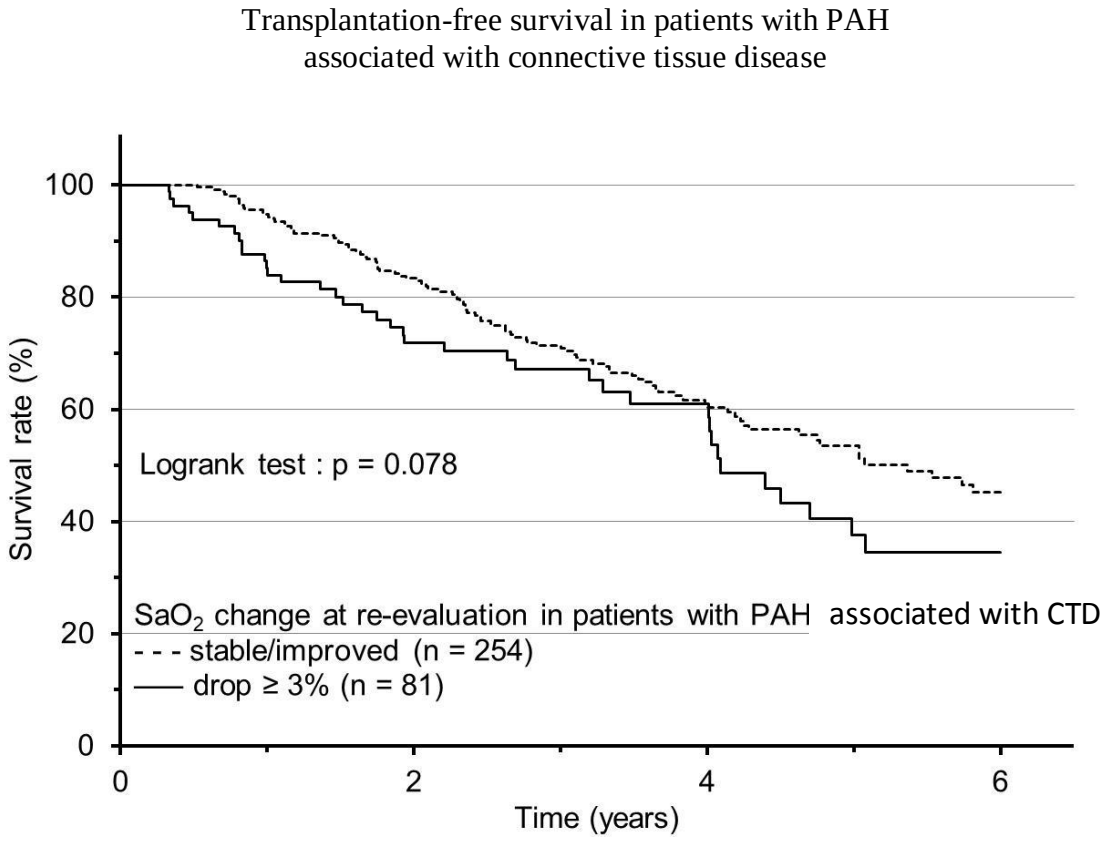
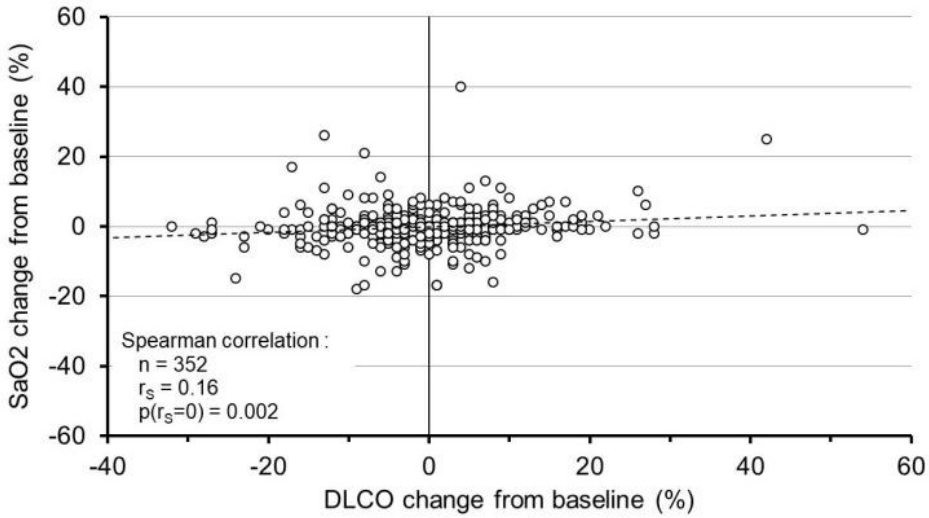


Figure S3: Correlation between SaO_2 and DL_{CO} changes from baseline.



DL_{CO}: diffusing capacity for carbon monoxide corrected for haemoglobin level; SaO_2: saturation of oxygen in arterial blood