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THE RIGHT HEART IN IDIOPATHIC PULMONARY FIBROSIS: IMPACT OF AGE AT DIAGNOSIS ON RIGHT VENTRICULAR–ARTERIAL COUPLING AND ON PROGNOSIS

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ABSTRACT

Introduction. Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disease of unknown cause, which mainly affects older adults and whose prognosis depends not only on the progression of fibrosis, but also on the involvement of the pulmonary circulation and of the right ventricle. Age is a recognised determinant of survival, included in the GAP index, whereas it is much less clear how the right ventricle responds, as age advances, to the increased load imposed by the pulmonary circulation. This study assessed the association of age at diagnosis with right heart function and with mortality, focusing on the coupling between the right ventricle and the pulmonary circulation.

Materials and methods. A total of 198 patients with IPF followed at the University Hospital of Modena were included in an ambispective observational study, with data collected in a dedicated database. Right ventricular function was assessed by tricuspid annular plane systolic excursion (TAPSE), vascular load by systolic pulmonary artery pressure (PAPs), and their coupling by the TAPSE/PAPs ratio. Patients were grouped by age at diagnosis (<65, 65–74 and ≥75 years). In all regression models, adjusted for sex and smoking, age was analysed as a continuous variable; in the mortality analysis it was also dichotomised at 65 years. Further models included both age and carbon monoxide diffusing capacity (DLCO).

Results. Mean age at diagnosis was 72.3 ± 8.2 years, with a male predominance (84.3%), and 55 patients (27.8%) died over a median follow-up of 44.6 months. No cross-sectional association was demonstrable between age at diagnosis and the severity of functional impairment, because lung function and echocardiographic parameters were similar across the three age groups, although a trend towards lower DLCO values was observed in older patients ($\rho = -0.126$; $p = 0.086$). After adjustment for sex and smoking, however, older age was independently associated with a lower TAPSE/PAPs ratio, available in 71 patients ($\beta = -0.010$ per year; $p = 0.034$), corresponding to a reduction of about 0.10 mm/mmHg every ten years, and the association persisted when DLCO was included in the model ($\beta = -0.011$; $p = 0.019$). No such association was found for TAPSE or PAPs alone. The association between age and survival was not gradual, since the year-by-year increase in risk was only borderline, whereas patients diagnosed at 65 years or older showed a markedly higher

probability of death (OR 8.00; 95% CI 1.83–34.98; p = 0.006). Patients who died were not older (p = 0.203), but had a worse cardiopulmonary profile, with a TAPSE/PAPs ratio of 0.41 ± 0.25 compared with 0.70 ± 0.35 in survivors (p < 0.001). When age and DLCO were considered together, DLCO remained the stronger predictor both of PAPs (p = 0.002) and of death (OR 0.98; p = 0.011), while age was independently associated only with the TAPSE/PAPs ratio.

Conclusion. In this cohort, patients diagnosed at an older age did not show a greater impairment of lung function but showed a reduced coupling between the right ventricle and the pulmonary circulation. Among the echocardiographic measures, only the TAPSE/PAPs ratio decreased independently with age, whereas TAPSE and PAPs alone did not. The ratio was also markedly lower in the patients who died, while DLCO remained the stronger prognostic marker in the cohort. The TAPSE/PAPs ratio, obtained from the echocardiographic assessment of the right heart, therefore adds information on right ventricular adaptation in older patients that pulmonary function tests alone do not provide. Larger prospective multicentre studies are needed to confirm these findings and to establish whether the systematic assessment of the TAPSE/PAPs ratio can improve the cardiological surveillance of these patients.

SOMMARIO

Introduzione. La fibrosi polmonare idiopatica (IPF) è una pneumopatia fibrosante progressiva a eziologia sconosciuta, tipica dell'età avanzata, la cui prognosi dipende non solo dalla progressione della fibrosi, ma anche dal coinvolgimento del circolo polmonare e del ventricolo destro. L'età è un determinante riconosciuto della sopravvivenza, compreso nell'indice GAP, mentre è molto meno chiaro come il ventricolo destro risponda, con l'avanzare dell'età, all'aumento del carico imposto dal circolo polmonare. Lo studio ha valutato l'associazione fra età alla diagnosi, funzione del cuore destro e mortalità, con particolare attenzione all'accoppiamento ventricolo-arterioso.

Materiali e metodi. Sono stati inclusi 198 pazienti con IPF dell'Azienda Ospedaliero-Universitaria di Modena, con disegno osservazionale ambispettivo e dati raccolti in un database dedicato. La funzione ventricolare destra è stata valutata con l'escursione sistolica del piano dell'anulus tricuspidale (TAPSE), il carico con la pressione arteriosa polmonare sistolica (PAPs) e l'accoppiamento con il rapporto TAPSE/PAPs. I pazienti sono stati suddivisi per età alla diagnosi (<65, 65–74 e ≥75 anni). In tutti i modelli di regressione, aggiustati per sesso e fumo, l'età è stata analizzata come variabile continua; nell'analisi della mortalità è stata inoltre dicotomizzata a 65 anni. Ulteriori modelli comprendevano età e capacità di diffusione del monossido di carbonio (DLCO).

Risultati. L'età media alla diagnosi era di 72,3 ± 8,2 anni, con prevalenza maschile (84,3%); nel follow-up mediano di 44,6 mesi sono deceduti 55 pazienti (27,8%). Non è emersa un'associazione trasversale dimostrabile fra età alla diagnosi e gravità della compromissione funzionale, poiché né la funzione respiratoria né i parametri ecocardiografici differivano fra le fasce d'età, pur con una tendenza a valori più bassi di DLCO nei più anziani ($\rho = -0{,}126$; $p = 0{,}086$). Dopo aggiustamento per sesso e fumo, tuttavia, un'età più avanzata si è associata in modo indipendente a un rapporto TAPSE/PAPs più basso, calcolabile in 71 pazienti ($\beta = -0{,}010$ per anno; $p = 0{,}034$), pari a una riduzione di circa 0,10 mm/mmHg ogni dieci anni, e l'associazione è persistita includendo la DLCO nel modello ($\beta = -0{,}011$; $p = 0{,}019$). Nessuna associazione analoga è emersa per il TAPSE né per la PAPs singolarmente. L'associazione fra età e sopravvivenza non è risultata graduale, poiché l'incremento anno per anno è rimasto ai margini della significatività, mentre i diagnosticati a 65

anni o più hanno mostrato una probabilità di morte nettamente maggiore (OR 8,00; IC 95% 1,83–34,98; p = 0,006). I deceduti non differivano per età (p = 0,203), ma presentavano un profilo cardiopolmonare peggiore, con rapporto TAPSE/PAPs di 0,41 ± 0,25 contro 0,70 ± 0,35 (p < 0,001). Considerando insieme età e DLCO, la DLCO è rimasta il predittore più forte sia della PAPs (p = 0,002) sia della mortalità (OR 0,98; p = 0,011), mentre l'età ha conservato un'associazione indipendente solo con il rapporto.

Conclusione. Nella coorte i pazienti diagnosticati in età più avanzata non presentavano una compromissione funzionale maggiore, ma mostravano un accoppiamento ridotto fra ventricolo destro e circolo polmonare. Fra i parametri ecocardiografici soltanto il rapporto TAPSE/PAPs si è ridotto in modo indipendente con l'età, mentre il TAPSE e la PAPs singolarmente no. Il rapporto era nettamente più basso anche nei pazienti deceduti, mentre fra le variabili considerate la capacità di diffusione è rimasta il principale indicatore prognostico. Il rapporto TAPSE/PAPs aggiunge quindi, sull'adattamento del ventricolo destro nei pazienti anziani, un'informazione che le prove di funzionalità respiratoria da sole non forniscono. Studi prospettici e multicentrici più ampi sono necessari per confermare questi risultati e per stabilire se la valutazione sistematica del rapporto possa migliorare la sorveglianza cardiologica di questi pazienti.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE-IPF	acute exacerbation of idiopathic pulmonary fibrosis
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
CI	confidence interval
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPFE	combined pulmonary fibrosis and emphysema
CpcPH	combined pre- and post-capillary pulmonary hypertension
CRP	C-reactive protein
CTEPH	chronic thromboembolic pulmonary hypertension
DLCO	diffusing capacity of the lung for carbon monoxide
DLCO/VA	diffusing capacity of the lung for carbon monoxide corrected for alveolar volume
DSP	desmoplakin
Ea	arterial elastance
Ees	end-systolic elastance
ERS	European Respiratory Society
ESC	European Society of Cardiology
ESR	erythrocyte sedimentation rate
FEV1	forced expiratory volume in the first second
FVC	forced vital capacity
GAP	Gender, Age, Physiology index
HIF-1α	hypoxia-inducible factor 1-alpha
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
IIP	idiopathic interstitial pneumonia
ILD	interstitial lung disease
IpcPH	isolated post-capillary pulmonary hypertension
IPF	idiopathic pulmonary fibrosis
IQR	interquartile range
JRS	Japanese Respiratory Society
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDD	multidisciplinary discussion
mPAP	mean pulmonary artery pressure

Abbreviation	Definition
OR	odds ratio
PAH	pulmonary arterial hypertension
PAPs	systolic pulmonary artery pressure
PAWP	pulmonary artery wedge pressure
PDGF-β	platelet-derived growth factor beta
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RDW	red cell distribution width
RHC	right heart catheterisation
SD	standard deviation
SLB	surgical lung biopsy
TAPSE	tricuspid annular plane systolic excursion
TBLC	transbronchial lung cryobiopsy
TGF-β	transforming growth factor beta
TLC	total lung capacity
UIP	usual interstitial pneumonia
VATS	video-assisted thoracoscopic surgery
VEGF	vascular endothelial growth factor
WU	Wood units
β	regression coefficient
ρ	Spearman rank correlation coefficient
R^2	proportion of the variance of the outcome explained by the model

1. IDIOPATHIC PULMONARY FIBROSIS

1.1 Definition and Classification

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown cause. It affects mainly older adults and carries a poor prognosis (1–3). The fibrotic process is limited to the lung and is not part of a systemic disease (3).

In classification terms, IPF belongs to the idiopathic interstitial pneumonias (IIP), a subgroup of the diffuse interstitial lung diseases (ILD), and it is the most common form among the IIP (1,4). Within the IIP, international classifications separate the chronic fibrosing forms, which include IPF, from the acute or subacute forms and from those related to cigarette smoking (4).

On imaging and under the microscope, IPF corresponds to the usual interstitial pneumonia (UIP) pattern. This pattern is defined by the spatial and temporal heterogeneity of the lesions: areas of preserved parenchyma alternate with areas of dense fibrosis, with fibroblastic foci in active proliferation and with areas of cystic remodelling, typically distributed in the lower lobes and under the pleura (1,3). A diagnosis of IPF therefore requires this pattern to be identified on high-resolution computed tomography (HRCT) or, when the HRCT findings are not conclusive, on lung biopsy, after the other known causes of interstitial lung disease have been excluded (3).

1.2 Epidemiology

IPF is a rare disease, but its incidence and prevalence are increasing (5). Two reasons lie behind this trend: greater diagnostic awareness and the ageing of the general population (5).

The estimates available in the literature differ widely from one another. A systematic review of 34 studies from 21 countries attributed this variability mainly to the different diagnostic criteria and data sources used in the individual studies (6). The most recent pooled analysis, which included populations from several continents, places the incidence between 0.9 and 13.0 cases per 100,000 inhabitants and the prevalence between 3.3 and 45.1 cases per 100,000 inhabitants (5).

Both incidence and prevalence rise with the age of the population considered (5). For every additional year of mean age, the prevalence of the disease increases by 6.2% (5).

From a demographic point of view, IPF typically affects people in the sixth and seventh decade of life (3), with a median age at diagnosis between 65 and 66 years (1,7). Onset below the age of 50 is rare and, when it occurs, calls for a careful differential diagnosis aimed at excluding an underlying connective tissue disease or a familial form (3,7). The distribution by sex shows a constant male predominance, with a male-to-female ratio between 1.5:1 and 1.7:1 (1).

Mortality attributed to IPF has also risen over time. In an analysis of ten countries, age-standardised mortality rates ranged between 4.68 and 13.36 cases per 100,000 inhabitants, and an increase was documented in every country considered (6).

Italian figures point in the same direction. The most recent study, based on health records of the Marche Region between 2014 and 2019, reported a mean incidence of 9.8 new cases per 100,000 inhabitants per year and a prevalence of 13.3 cases per 100,000 residents(8). Over the same period the annual increase was 6%, with higher rates in men and in older subjects(8). Similar estimates had already been reported in earlier studies from Lombardy and Lazio (9,10).

1.3 Causes and Pathogenesis

1.3.1 Risk Factors

The cause of IPF remains, by definition, unknown. Several factors that increase the risk of developing it have nonetheless been identified, and they are related either to the patient or to the environment (1,11).

Among the factors related to the patient, age has the leading role. This is not a simple association with chronological age. Cellular ageing, with telomere shortening, and the progressive loss of the regenerative capacity of the alveolar epithelium are part of the mechanism that leads to fibrosis (11). Male sex is also associated with a higher risk, as shown by the constant male predominance observed in the studies published so far (1).

The second factor related to the patient is genetic predisposition. The polymorphism in the promoter of the MUC5B gene, which encodes a mucin secreted by the airway epithelium, is the strongest known genetic risk factor and is present in 38% of patients with IPF (11,12). Compared with non-carriers, the risk of disease is about nine times higher in heterozygotes and about twenty-two times higher in homozygotes (12). This polymorphism has been linked to an excess production of mucin and to the resulting impairment of mucociliary clearance (11). Next in importance comes the desmoplakin gene (DSP), which is involved in the adhesion between alveolar epithelial cells (11).

Alongside the sporadic forms there are familial forms of the disease, and a family history of interstitial lung disease is one of the recognised risk factors for IPF (3). Their frequency varies considerably and is around 5-20% (11). Transmission is typically autosomal dominant with reduced penetrance, but these forms often go unrecognised in clinical practice (1).

The distinction between sporadic and familial forms does not correspond, however, to a clear genetic separation. The MUC5B polymorphism has been identified as a risk factor in both (12), and mutations in the genes that regulate telomere length and in those of the surfactant proteins are described mainly in the familial forms, although they are also found, more rarely, in sporadic cases (11).

On the environmental side, cigarette smoking is the factor most consistently associated with IPF (1,7). Follow occupational exposures, in particular to metal and wood dust, but also to agricultural chemicals, stone and sand(1,11). Chronic exposure to air pollutants is associated with a higher incidence of disease and, in patients who are already affected, with an increased risk of exacerbation, of decline in forced vital capacity (FVC), of progression and of death(13). Gastro-oesophageal reflux is among the contributing factors because of the possible role of chronic microaspiration in alveolar epithelial damage (3,11). Finally, some chronic viral infections are also considered environmental risk factors, among them those caused by Epstein-Barr virus and hepatitis C virus (3).

1.3.2 Pathogenic Mechanisms

IPF was historically regarded as a primarily inflammatory disease, in which chronic inflammation of the lung parenchyma progressively evolved towards fibrosis (7).

This model has been progressively abandoned for two reasons. The first is that anti-inflammatory and immunosuppressive treatments proved ineffective and, in some cases, even harmful (7). The second is that evidence accumulated in favour of a different mechanism, now considered the reference model, in which an aberrant response to tissue repair takes place and the contribution of inflammation is relatively marginal (1,7).

According to this model, the pathogenic process starts from damage to the alveolar epithelium caused by environmental factors (1). The damage arises in a multifocal way, in single bronchiolo-alveolar units, and at different moments in time (12). It is precisely the repeated and non-synchronous nature of the damage that accounts for the spatial and temporal heterogeneity of the UIP pattern (1).

In a genetically predisposed and biologically aged subject, repeated damage is not repaired effectively (11). Cellular senescence, mitochondrial dysfunction, endoplasmic reticulum stress and altered autophagy impair the regenerative capacity of the epithelium and lead to a dysfunctional repair programme (11).

The aberrant repair response translates into the activation and uncontrolled proliferation of resident fibroblasts. These differentiate into myofibroblasts, the cells responsible for the production and excessive deposition of extracellular matrix that characterises fibrotic tissue (1,7).

The main molecular mediator of this step is TGF-β (transforming growth factor-β), considered the central regulator of fibrosis. In IPF, TGF-β is expressed by alveolar epithelial cells and by alveolar macrophages, and its expression is located at the fibroblastic foci (11). The process is further amplified by signalling pathways typically involved in embryonic lung development, such as the Wnt/β-catenin pathway, which are excessively activated (11).

Once it has started, fibrosis tends to be self-sustaining (11). Fibroblasts sense, through integrins, the stiffness of the matrix that they themselves have produced, and this increase in stiffness then drives the differentiation and activation of myofibroblasts

(11). The result is a progressive and irreversible architectural remodelling of the lung parenchyma (1).

RNA sequencing techniques were introduced later and, by quantifying gene expression in single cells, made it possible to identify cell populations that were not previously known (11).

On this basis an epithelial population named aberrant basaloid cells has been identified (14). These cells express basal epithelial, mesenchymal and senescence markers at the same time, are located specifically at the edge of the fibroblastic foci and appear to contribute to fibroblast activation, partly through the release of TGF-β (14). The same techniques have also shown that fibroblasts and myofibroblasts in IPF are not a cell type distinct from the normal one, and that the expression of extracellular matrix genes is increased in all the populations analysed (11).

Overall, the view that emerges today is that of a disease triggered by epithelial damage in which, however, several cell types (epithelium, mesenchyme, endothelium and immune cells) interact in producing and maintaining the fibrotic phenotype (11). The sequence of events is shown in Figure 1.

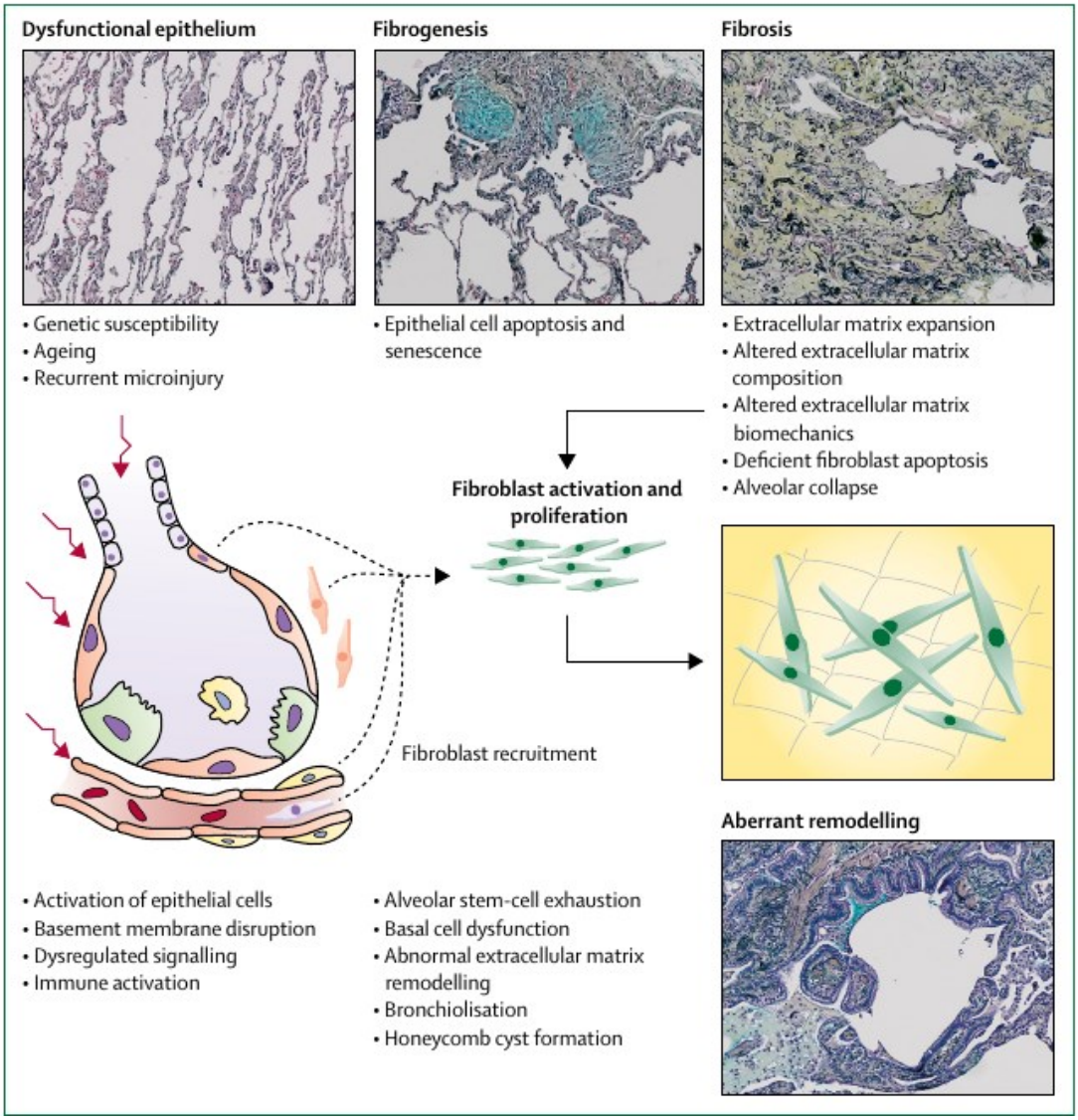


Figure 1. Proposed mechanisms in the pathogenesis of idiopathic pulmonary fibrosis.
Recurrent microinjury to a genetically susceptible and aged alveolar epithelium causes apoptosis and senescence of the epithelial cells; recruitment, activation and proliferation of fibroblasts follow, together with expansion and biomechanical alteration of the extracellular matrix and, finally, aberrant remodelling with the formation of honeycomb cysts. From (7).

1.4 Clinical Features

1.4.1 Clinical Presentation

The clinical onset of IPF is typically insidious, and for this reason patients come to medical attention months, and sometimes years, after the first symptoms appear (1). The clinical presentation is dominated by progressive dyspnoea on exertion, which may be accompanied by a chronic dry cough (7). These symptoms are non-specific and are at first attributed to ageing, to reduced exercise tolerance or to other coexisting

conditions such as previous smoking, emphysema, heart disease or obesity (1,7). For this very reason an adequate clinical suspicion is essential in order to avoid diagnostic delay (7).

Less often the onset is acute, with progressive respiratory worsening over days or weeks, accompanied by fever and influenza-like symptoms (7). In these cases, a careful differential diagnosis with other forms of acute interstitial lung disease is needed (7).

On chest examination, fine, high-pitched inspiratory crackles are typically heard at both lung bases, and are described as velcro crackles (1,7). Finger clubbing is present in about 30% of patients (7). It is also essential to look carefully for clinical signs of an underlying connective tissue disease, in particular systemic sclerosis, Sjögren syndrome, myositis, rheumatoid arthritis and vasculitis, since their presence points towards an alternative diagnosis (3,7).

1.4.2 Comorbidities

Comorbidities are particularly common and cover a wide range of conditions, both respiratory and extrapulmonary, with considerable variability in the prevalence estimates reported by individual studies (15). Among the respiratory comorbidities, pulmonary hypertension (3-86%) is one of the most important, because it is independently associated with a higher risk of death (15). Chronic obstructive pulmonary disease and emphysema (6-67%) also affect prognosis significantly: together with lung cancer (3-48%), they are associated with the highest mortality among all the comorbidities considered (15). The coexistence of emphysema and IPF defines combined pulmonary fibrosis and emphysema (CPFE), which exposes the patient to a greater risk of developing pulmonary hypertension and, for this reason, to a further increase in mortality (15). Obstructive sleep apnoea syndrome (6-91%) is also frequently found at lung level (15).

Among extrapulmonary comorbidities, gastro-oesophageal reflux disease (0-94%) is more common than in the general population (15). Cardiovascular conditions are also widely represented, such as ischaemic heart disease, arrhythmias, heart failure, systemic arterial hypertension and cerebrovascular disease (15). Among metabolic conditions, diabetes mellitus is the one most often reported, with a prevalence between

10% and 33%, followed by dyslipidaemia and by disorders of body weight (15). Timely recognition and management of these associated conditions play a clinically relevant part in defining the overall prognosis of the patient with IPF (15).

1.5 Diagnostic Work-Up

The diagnosis of IPF rests on a process of exclusion and on the multidisciplinary integration of clinical, radiological and, when needed, histopathological data (3). Exclusion is necessary because the UIP pattern is not specific to IPF. The same pattern can be seen in chronic hypersensitivity pneumonitis, in asbestosis, in connective tissue disease-associated interstitial lung disease and in drug-induced lung toxicity (7). The other idiopathic interstitial pneumonias and the interstitial lung diseases related to domestic or occupational exposures must also be distinguished (3,7).

1.5.1 History Taking and Laboratory Tests

The work-up begins with history taking. The guidelines recommend a detailed history both drugs taken and of environmental exposures at home, at work and in the places the patient regularly visits (3). The aim is to identify exposures able to cause interstitial lung disease, such as moulds, birds, feathers, animal breeding, metal or wood dust, and drugs that are potentially toxic to the lung, to exclude hypersensitivity pneumonitis first of all (3).

Serological assessment follows and is recommended in all patients with newly detected interstitial lung disease in order to exclude a connective tissue disease (3). The first-line panel includes C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies tested by immunofluorescence, rheumatoid factor, a myositis panel and anti-cyclic citrullinated peptide antibodies (3). When clinical or serological findings raise suspicion, the work-up is extended with more specific tests directed towards systemic sclerosis, Sjögren syndrome or vasculitis (3).

1.5.2 Pulmonary Function Tests

In established disease, pulmonary function tests show a restrictive ventilatory defect with a reduction in total lung capacity (TLC) and impaired gas exchange with a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) (7). In the early stages, or when coexisting emphysema pseudo-normalises lung volumes,

spirometry and plethysmography may be normal and the only detectable abnormality is an isolated reduction in diffusing capacity (7).

1.5.3 Radiological Diagnosis

Once the other known causes have been excluded, the central investigation is chest HRCT, which allows the parenchymal findings to be assigned to one of four categories: typical UIP, probable UIP, indeterminate for UIP, and findings suggestive of an alternative diagnosis (3).

The typical UIP pattern has a mainly basal and subpleural distribution, often uneven, and shows honeycombing with or without peripheral traction bronchiectasis and bronchiolectasis (3). The term honeycombing indicates clustered cystic air spaces of typically uniform diameter, with thick and well-defined walls, arranged beneath the pleura in one or more layers (3). Traction bronchiectasis and bronchiolectasis, on the other hand, consist of irregular dilatation of the airways, pulled outwards by the surrounding fibrotic tissue until they become markedly distorted (3). Honeycombing is the discriminating finding: its presence is required in order to define a typical UIP pattern on imaging (3). An example is shown in Figure 2.

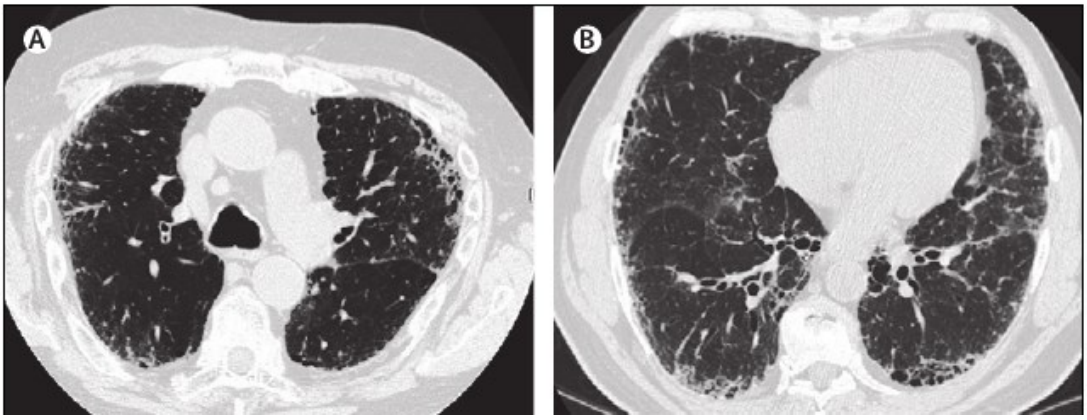


Figure 2. UIP pattern on high-resolution computed tomography.
Subpleural reticular opacities and honeycombing with basal predominance and uneven distribution (A, B). From(1).

The probable UIP pattern shares the same basal and subpleural distribution but is characterised by reticular changes with peripheral traction bronchiectasis or bronchiolectasis in the absence of honeycombing (3). The findings are instead defined as indeterminate for UIP when fibrosis is more subtle, with mild reticulation and

minimal architectural distortion, or when the findings and their distribution do not point to any specific cause (3).

The fourth category includes the findings that suggest a different diagnosis, in which HRCT does not simply exclude IPF but points towards another condition (3).

1.5.4 Histopathological Assessment

It is the radiological pattern that determines whether further investigations are needed. When a typical UIP pattern is present in a patient with an appropriate clinical context, the guidelines recommend performing neither cellular analysis of bronchoalveolar lavage fluid nor any type of lung biopsy (3). When the pattern is probable UIP, indeterminate or suggestive of an alternative diagnosis, cellular analysis of bronchoalveolar lavage fluid and surgical lung biopsy are suggested instead (3).

Histological samples can be obtained in different ways. Surgical lung biopsy (SLB) provides large and representative samples and is today performed preferably by video-assisted thoracoscopy (VATS) rather than by open thoracotomy, in patients who tolerate single-lung ventilation (3). In subjects with severe functional impairment or relevant comorbidities, the risks of the procedure may outweigh its benefits, and the decision has to be adjusted to the clinical situation of the individual patient (3). Sampling from two or three different lobes is also recommended, because the histological findings may differ between segments of the same lung (3).

As an alternative, transbronchial cryobiopsy (TBLC) is a less invasive option and has been recognised as acceptable in centres with adequate experience. The smaller size of the samples, however, carries a greater risk of sampling error and calls for more caution in interpreting the result (16).

Histologically, the UIP pattern is defined, already at low magnification, by dense fibrosis with a non-uniform distribution alternating with areas of less affected parenchyma, and with more marked involvement of the subpleural and paraseptal regions (3). Fibrosis distorts the lung architecture and often produces microscopic honeycombing, made of cystic spaces lined by bronchiolar epithelium (3). Inflammation is generally limited, whereas fibroblastic foci, that is small areas

containing actively proliferating fibroblasts and myofibroblasts, are a constant finding (3). The histological appearance is shown in Figure 3.

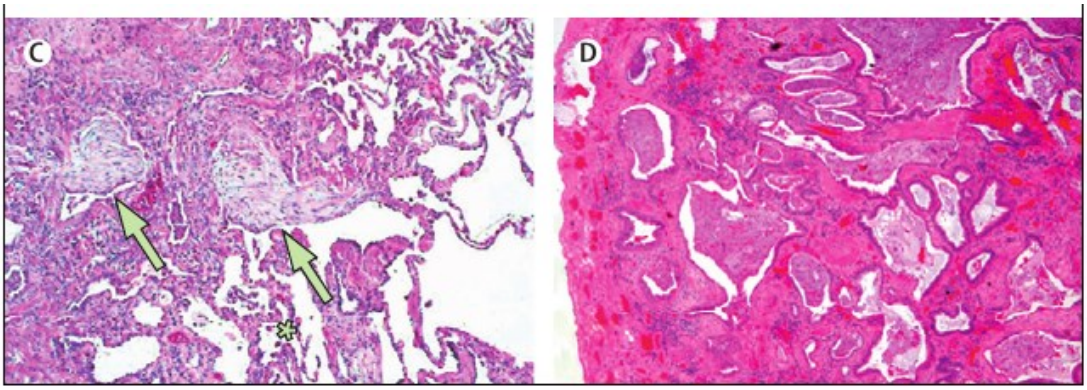


Figure 3. UIP pattern on histopathological examination.
On the left, temporal heterogeneity: areas of altered parenchyma and preserved areas lie side by side without transition zones; the arrows indicate fibroblastic foci and the asterisk an area of relatively spared parenchyma. On the right, an area of microscopic honeycombing, with cystic spaces lined by bronchiolar epithelium. From (1).

The Fleischner Society has proposed a diagnostic scheme that differs from the one in the ATS/ERS/JRS/ALAT guidelines and widens the situations in which HRCT alone, in the appropriate clinical context, is enough to diagnose IPF. Under this scheme a probable UIP pattern is also considered conclusive, which makes it possible to reduce the number of patients sent for biopsy procedures (17).

1.5.5 Multidisciplinary Assessment

Whichever scheme is adopted, multidisciplinary discussion, which involves the pulmonologist, the radiologist and, where appropriate, the pathologist, is today the reference standard for the diagnosis of IPF (3,18). Discussion between specialists increases diagnostic confidence and there is also evidence that a diagnosis made in a multidisciplinary setting predicts the course of the disease more consistently than one made by individual specialists (18).

The overall sequence of investigations is summarised in Figure 4.

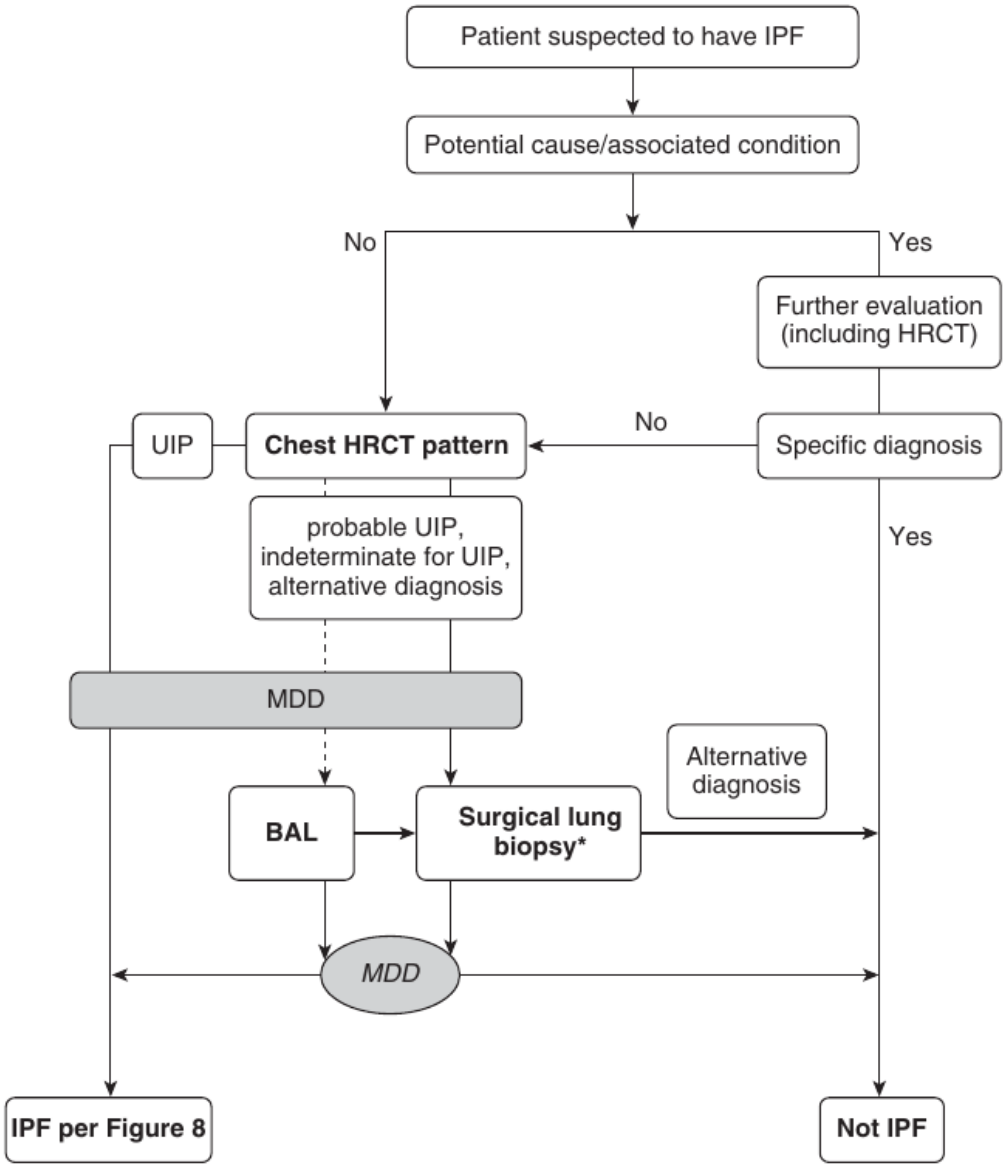


Figure 4. Diagnostic algorithm for idiopathic pulmonary fibrosis.
In the patient with suspected IPF, causes or associated conditions are looked for first; in their absence the pathway is guided by the HRCT pattern, which leads either to a direct diagnosis or to bronchoalveolar lavage and surgical lung biopsy. Multidisciplinary discussion (MDD) takes place at both decision points. The reference IPF per Figure 8 corresponds, in the original document, to the table combining radiological and histological patterns. From (3).

1.6 Natural History and Exacerbations

The clinical course of IPF is heterogeneous and not always predictable. Some patients show a slow and gradual functional decline, others a more rapid progression, and others again a relatively stable course that may be interrupted by episodes of acute

respiratory deterioration (7,16). The different disease trajectories are shown in Figure 5.

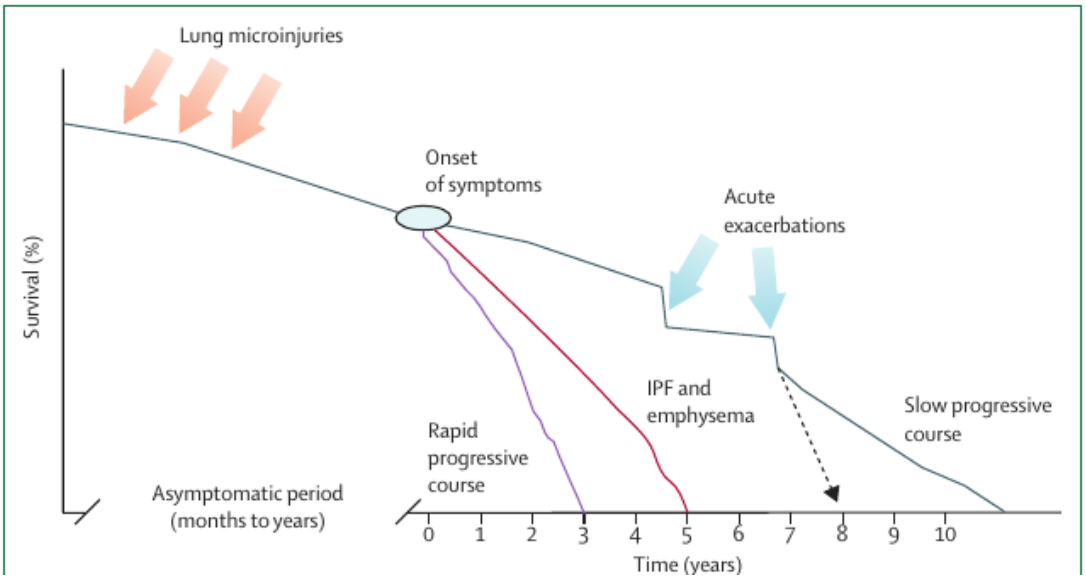


Figure 5. Clinical phenotypes and natural history of idiopathic pulmonary fibrosis.
An asymptomatic period of months or years, sustained by repeated lung microinjury, is followed by the appearance of symptoms. Most patients show a slowly progressive decline; a minority follow a rapidly progressive course, while coexisting emphysema is associated with shorter survival. Acute exacerbations appear as sudden drops in the survival curve. From(1).

Acute exacerbations of IPF (AE-IPF) are defined as episodes of acute and clinically significant respiratory deterioration, with worsening dyspnoea typically lasting less than one month (19). On imaging they are characterised by new ground-glass opacities or bilateral consolidations, in addition to the underlying fibrotic changes, which are not fully explained by heart failure or fluid overload (19).

The histological substrate of the event is diffuse alveolar damage added to the pre-existing fibrosis with a UIP pattern (19). An exacerbation therefore does not end with the acute episode, and the event may in turn accelerate the chronic mechanisms that sustain the fibrotic process (19).

Exacerbations may be idiopathic or triggered by identifiable factors, such as respiratory infections, episodes of microaspiration or surgical procedures (19). Their prognostic weight is considerable, since in most series in-hospital mortality exceeds 50% and median survival after the event is about 3-4 months (19). About 46% of deaths from IPF are preceded by an exacerbation (19).

1.7 Prognosis

IPF carries a severe prognosis. Without treatment, median survival from diagnosis is between 2 and 4 years, a figure that places this disease among the interstitial lung diseases with the least favourable course (7).

The individual variability of the clinical course has made it necessary to identify prognostic tools able to stratify the risk of death at the time of diagnosis. The GAP index (Gender, Age, Physiology) was developed and validated for this purpose. It is a score that combines sex, age and two pulmonary function parameters, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO)(20). The total score assigns patients to three stages of increasing severity, with a one-year mortality of 6%, 16% and 39% respectively (20). Derived in a United States cohort and later validated in independent cohorts, the GAP index is today a simple and reproducible tool for the prognostic stratification of patients with IPF(20).

There are also single factors that contribute to defining a patient's prognosis, such as age at diagnosis, the severity of pulmonary functional impairment, the presence of comorbidities and the occurrence of acute exacerbations (11,15,19).

How early the diagnosis is made is also important. Diagnostic delay in IPF, defined as the interval between symptom onset and definitive diagnosis, has been estimated at a median of about 2.1 years, and male sex, as well as older age, are independent risk factors for it (21). A delay longer than one year is independently associated with significantly worse progression-free survival, with lower quality of life and with a higher hospitalisation rate (22).

1.8 Treatment

1.8.1 Drug Treatment

Until the early 2010s no drug treatment was able to change the natural history of IPF (7). The introduction of antifibrotic agents was a turning point, although none of the drugs available today can stop or reverse the fibrotic process, they can only slow its progression (7). Two molecules, nintedanib and pirfenidone, are currently recommended as first-line treatment in patients with IPF (16).

Nintedanib is a tyrosine kinase inhibitor and acts by simultaneously blocking several receptors involved in the pathogenesis of fibrosis, among them those for fibroblast growth factor, platelet-derived growth factor and vascular endothelial growth factor (7). The phase III registration trial INPULSIS demonstrated its efficacy, with a significant reduction in the annual rate of FVC decline compared with placebo (23).

Pirfenidone is an orally administered pyridine with combined anti-inflammatory, antioxidant and antifibrotic activity. Its precise mechanism of action is not known, but in experimental models the drug regulates TGF-β and inhibits fibroblast proliferation and collagen synthesis (7). The phase III ASCEND trial documented a significantly smaller decline in FVC at 52 weeks in the treated group than in the placebo group (24).

The two molecules have a comparable effect on the rate of FVC decline at one year, which is roughly halved compared with placebo (7). Neither has prospectively demonstrated a survival benefit, although both show a trend in that direction (7). The choice between the two drugs is therefore guided mainly by the safety profile and by tolerability in the individual patient (7).

Since the disease is chronic and invariably progressive, treatment should be started at the time of diagnosis (7). The registration trials, however, enrolled patients with mild to moderate functional impairment, whereas efficacy data in more advanced forms are limited (7).

Both drugs have an acceptable safety profile, but about one fifth of patients stop treatment because of side effects or disease progression (7). The main safety issue is a rise in transaminases, which calls for periodic monitoring of liver function; pirfenidone is also associated with gastrointestinal disturbances and skin photosensitivity, and nintedanib mainly with diarrhoea (7). Side effects generally respond to a temporary dose reduction or to stopping the drug (7).

1.8.2 Overall Management and Treatment of Complications

Alongside drug treatment, the management of the patient with IPF includes several supportive measures (16). Oxygen therapy should be considered in hypoxaemic patients, while pulmonary rehabilitation improves dyspnoea and quality of life and

may improve functional status (7,16). In advanced disease there is a role for symptom control, of dyspnoea and cough, and for the involvement of palliative care in planning end-of-life decisions (7).

In eligible subjects with advanced disease, lung transplantation should be considered, since in selected patients it improves quality of life and prolongs survival, which is around 50% at five years after transplantation (7). Referral to the transplant centre should take place early (7).

Acute exacerbations may be treated with corticosteroids, whereas mechanical ventilation is not recommended in most patients with respiratory failure (16).

One essential component of management concerns associated conditions. The guidelines recommend that patients with IPF be assessed and treated for the comorbidities present, and they explicitly mention pulmonary hypertension, gastro-oesophageal reflux, obstructive sleep apnoea and lung cancer (16).

Among these complications, pulmonary hypertension is one of the most frequent, affects survival independently and calls for a cardiological assessment that goes beyond pulmonary evaluation alone (15).

2. PULMONARY HYPERTENSION

2.1 Background

2.1.1 Epidemiology

Pulmonary hypertension is a pathophysiological condition whose diagnosis requires right heart catheterisation (25). The 2022 ESC/ERS guidelines specify, however, that the haemodynamic definition, although it is the core of the characterisation, does not exhaust the diagnostic process, because the final diagnosis and the assignment to a clinical group must reflect the whole clinical context and take account of the echocardiographic findings, of pulmonary function and of chest imaging (25).

In epidemiological terms this is anything but a rare entity: the estimated prevalence is around 1% of the world population (25,26). Contrary to what the specialist literature might suggest, since it is largely devoted to the rare forms, the great majority of cases have common causes: left heart disease is the most frequent cause worldwide, followed by lung disease and in particular by chronic obstructive pulmonary disease (25,26).

Whatever the underlying condition, the appearance of pulmonary hypertension leads to worse symptoms and to increased mortality (25).

Pulmonary hypertension affects all age groups, but it becomes increasingly important in the elderly population, with a rise in prevalence beyond the age of 65 (25). Demographic ageing is in fact producing a marked change in the distribution and in the phenotypic profile of the patients who come to medical attention (26). Registries document this shift clearly: a condition long regarded as typical of the young and mainly female patient is today frequently diagnosed in older patients with cardiovascular comorbidities and a median age at diagnosis of 60 years (26). Age also behaves as an independent predictor of survival (27).

2.1.2 Haemodynamic Definition

Pulmonary hypertension is defined as a mean pulmonary artery pressure above 20 mmHg at rest. This value comes from invasive measurement in healthy subjects, in whom mean pressure at rest is around 14 mmHg, and it corresponds to the 97.5th percentile of the distribution observed (25,28–30).

Mean pressure alone is not enough to characterise the condition, because a rise in that value may result from very different mechanisms. For this reason, the definition includes two further parameters, both obtained during the same catheterisation: pulmonary capillary wedge pressure and pulmonary vascular resistance (25).

Pulmonary capillary wedge pressure (PAWP) is obtained by temporarily occluding a branch of the pulmonary artery with a balloon catheter: once flow has been interrupted, the tip of the catheter records a pressure value that corresponds to left atrial pressure (28). A raised PAWP indicates that the pressure increase in the pulmonary circulation is transmitted passively backwards from the left side of the heart, as typically happens in heart failure and in valvular disease (31). The threshold value for wedge pressure is set by the ESC/ERS guidelines at 15 mmHg (25).

Pulmonary vascular resistance (PVR) expresses instead how much the pulmonary vessels resist blood flow and is obtained by relating the pressure drop across the pulmonary circulation to cardiac output, according to the formula (mPAP − PAWP)/CO (25). An increase in PVR places the cause of pulmonary hypertension at the level of the pulmonary vascular structures (25). The ESC/ERS guidelines set the PVR threshold at 2 Wood units and identify this value both as the upper limit of normal and as the lowest prognostically relevant threshold (25).

Combining the three parameters makes it possible to distinguish (Table 1) pre-capillary PH, isolated post-capillary PH and combined pre- and post-capillary PH, in which the two conditions coexist.

Table 1. Haemodynamic definitions of pulmonary hypertension according to the 2022 ESC/ERS guidelines.

Definition	Haemodynamic features
Pulmonary hypertension	mPAP > 20 mmHg
Pre-capillary PH	mPAP > 20 mmHg; PAWP ≤ 15 mmHg; PVR > 2 WU
Isolated post-capillary PH (IpcPH)	mPAP > 20 mmHg; PAWP > 15 mmHg; PVR ≤ 2 WU
Combined pre- and post-capillary PH (CpcPH)	mPAP > 20 mmHg; PAWP > 15 mmHg; PVR > 2 WU
Exercise PH	mPAP/cardiac output slope between rest and exercise > 3 mmHg/L/min

mPAP: mean pulmonary artery pressure; PAWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units. (25)

Pulmonary hypertension is also defined as unclassified when pulmonary pressure above 20 mmHg is found together with normal resistance and wedge pressure, without meeting the criteria either of the pre-capillary or of the post-capillary form. These are generally conditions sustained by an increase in pulmonary blood flow, for which clinical follow-up and further investigation of the cause are recommended (25).

The 2022 guidelines also reintroduce exercise pulmonary hypertension, defined by a disproportionate rise in pulmonary pressure relative to the increase in cardiac output during exercise. It identifies an abnormal haemodynamic response in patients who are still normal at rest (25).

2.2 Clinical Classification

The clinical classification proposed by the 2022 ESC/ERS guidelines is based on several elements: the mechanism through which pulmonary hypertension develops, the way it presents clinically, the associated clinical conditions, the haemodynamic profile that characterises it and the treatment it requires (25). Five different groups are obtained in this way, and their relative frequency is shown in Figure 6:

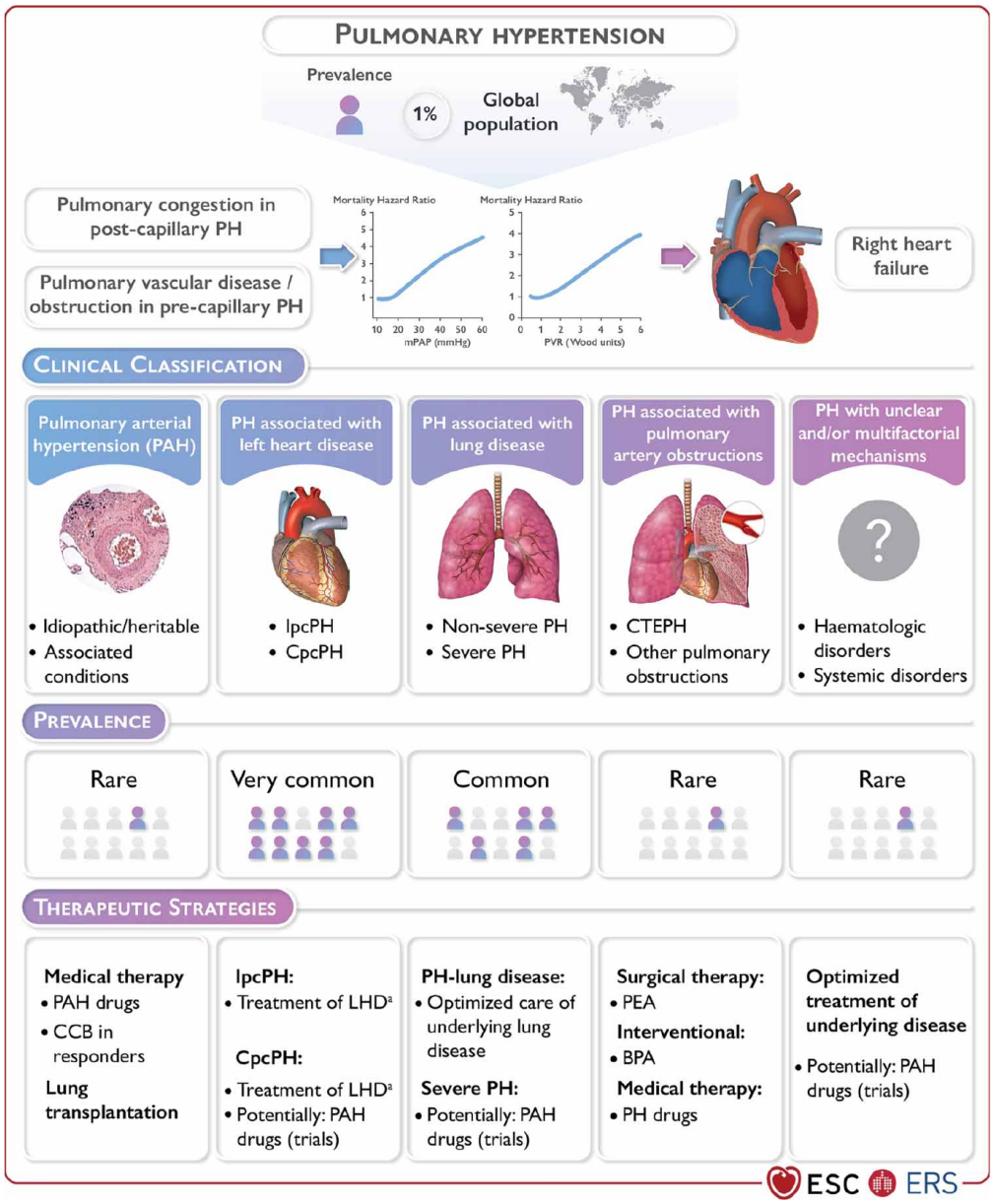


Figure 6. Overview of pulmonary hypertension: prevalence in the general population, division into the five clinical groups and relative frequency of each of them.

The lower part of the figure, which concerns treatment strategies, falls outside the topics covered in this chapter. From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

1. Group 1, Pulmonary Arterial Hypertension: this group includes the pre-capillary forms in the absence of other causes of pre-capillary PH such as chronic thromboembolic pulmonary hypertension (CTEPH) or PH associated with lung disease. It also includes idiopathic pulmonary hypertension, which in most registries accounts for slightly more than half of the cases, together with the heritable form, the forms associated with drugs and toxins, and those associated

with connective tissue disease, HIV infection, portal hypertension, congenital heart disease and schistosomiasis (25). It is a rare group, but it is also the only one for which an established specific drug treatment exists (25).

2. Group 2, Pulmonary Hypertension Associated with Left Heart Disease: this is by far the most frequent group and is characterised by a post-capillary haemodynamic profile (25). In most cases it is the consequence of an underlying cardiac disease, and results from the passive increase in the filling pressures of the left heart and in left atrial pressure (31). It mainly affects older patients and complicates at least half of the cases of heart failure with preserved ejection fraction. It is also common in left-sided valvular disease, where its prevalence increases with the severity of the lesion (25).
3. Group 3, Pulmonary Hypertension Associated with Lung Disease and/or Hypoxia: this is the second most frequent group and, like the first, has a pre-capillary profile (25). As can be seen in the table (Figure 7), the subgroups are not defined by individual disease but by respiratory functional pattern: obstructive lung diseases are distinguished from restrictive ones, which include idiopathic pulmonary fibrosis, and from those with a mixed pattern, alongside hypoventilation syndromes, hypoxia without lung disease and developmental lung disorders (25). By convention, the name of PH associated with lung disease places the name of the lung disease before the abbreviation for pulmonary hypertension, since it is usually the lung disease that appears first, and this is where the labels in current use come from (for example COPD-PH, IPF-PH) (32).
4. Group 4, Pulmonary Hypertension Associated with Pulmonary Artery Obstruction: this includes essentially the chronic thromboembolic form, alongside rarer causes of obstruction such as tumours, arteritis and congenital stenosis; the haemodynamic profile is usually pre-capillary, although a post-capillary component may also be present (25). It is an uncommon condition, but it is being diagnosed more often thanks to greater clinical awareness and to active screening in patients who still have dyspnoea after a pulmonary embolism (25).
5. Group 5, Forms with Unclear or Multifactorial Mechanisms: this includes the forms in which pulmonary hypertension may depend on increased pre-capillary

pressures, on increased post-capillary pressures or on a direct effect on the pulmonary vessels, and in which the haemodynamic profile is therefore variable. It covers heterogeneous conditions, from haematological and metabolic disorders to chronic kidney failure, and for most of them incidence and prevalence remain unknown (25).

TABLE 6 Clinical classification of pulmonary hypertension

GROUP 1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.1.1 Non-responders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable[a]
1.3 Associated with drugs and toxins[a]
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
GROUP 2 PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction[b]
2.2 Valvular heart disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 PH associated with lung diseases and/or hypoxia
3.1 Obstructive lung disease or emphysema
3.2 Restrictive lung disease
3.3 Lung disease with mixed restrictive/obstructive pattern
3.4 Hypoventilation syndromes
3.5 Hypoxia without lung disease (*e.g.* high altitude)
3.6 Developmental lung disorders
GROUP 4 PH associated with pulmonary artery obstructions
4.1 Chronic thrombo-embolic PH
4.2 Other pulmonary artery obstructions[c]
GROUP 5 PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders[d]
5.2 Systemic disorders[e]
5.3 Metabolic disorders[f]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

HF, heart failure; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. [a]Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders. [b]Left ventricular ejection fraction for HF with reduced ejection fraction: ⩽40%; for HF with mildly reduced ejection fraction: 41–49%. [c]Other causes of pulmonary artery obstructions include: sarcomas (high or intermediate grade or angiosarcoma), other malignant tumours (*e.g.* renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), non-malignant tumours (*e.g.* uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis. [d]Including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders. [e]Including sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1. [f]Including glycogen storage diseases and Gaucher disease.

Figure 7. Clinical classification of pulmonary hypertension, with the complete list of the conditions included in each of the five groups.

From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

It should finally be considered that assignment to a group is not always easy, and that the difficulty is greatest in the older patient. All groups may in fact have both a pre-capillary and a post-capillary component, and more than one predisposing condition may coexist in the same patient; the classification therefore has to be based on the cause that is presumed to be predominant (25).

2.3 Clinical Features

The symptoms of pulmonary hypertension come largely from right ventricular dysfunction and, in the early stages, appear only during physical effort (25). The initial presentation is non-specific and easily attributed to other causes, and it becomes clearly recognisable only when right ventricular dysfunction is clinically manifest, which typically happens at an advanced stage (25). A documented diagnostic delay follows from this. The time between symptom onset and diagnosis remains longer than two years and most patients come to medical attention with disease that is already advanced (25). In the REVEAL registry about one patient in five had reported symptoms for more than two years before recognition (33). A wait longer than two years, according to an Australian and New Zealand series, is associated with worse survival, with an 11% increase in the risk of death even after adjustment for age, sex and disease subtype (34).

The symptoms most often reported include the following, listed in Figure 8 from the early to the advanced stages of the disease:

- **Exertional dyspnoea**: this is the cardinal symptom, appears with progressively smaller efforts and is reported by about 86% of patients at presentation (25,33). One variant is bendopnoea, that is dyspnoea that appears when bending forward (25);
- **Fatigue and rapid exhaustion**: this is the second most frequent symptom, reported by about a quarter of patients (25,33);
- **Palpitations** and haemoptysis (25);
- **Syncope**, typically during or immediately after physical exertion (25);

- **Abdominal distension and nausea induced by exercise, and weight gain from fluid retention**: these express the systemic congestion that follows right ventricular failure and therefore appear in the more advanced stages (25);
- **Symptoms from pulmonary artery dilatation**: these are rare and result from compression of the adjacent structures by the dilated vessel (25). They include:
    - chest pain on exertion, from dynamic compression of the left main coronary artery (25);
    - hoarseness, from compression of the left recurrent laryngeal nerve, a condition known as cardiovocal or Ortner syndrome (25);
    - dyspnoea, wheeze, cough, lower respiratory tract infections and atelectasis, from bronchial compression (25).

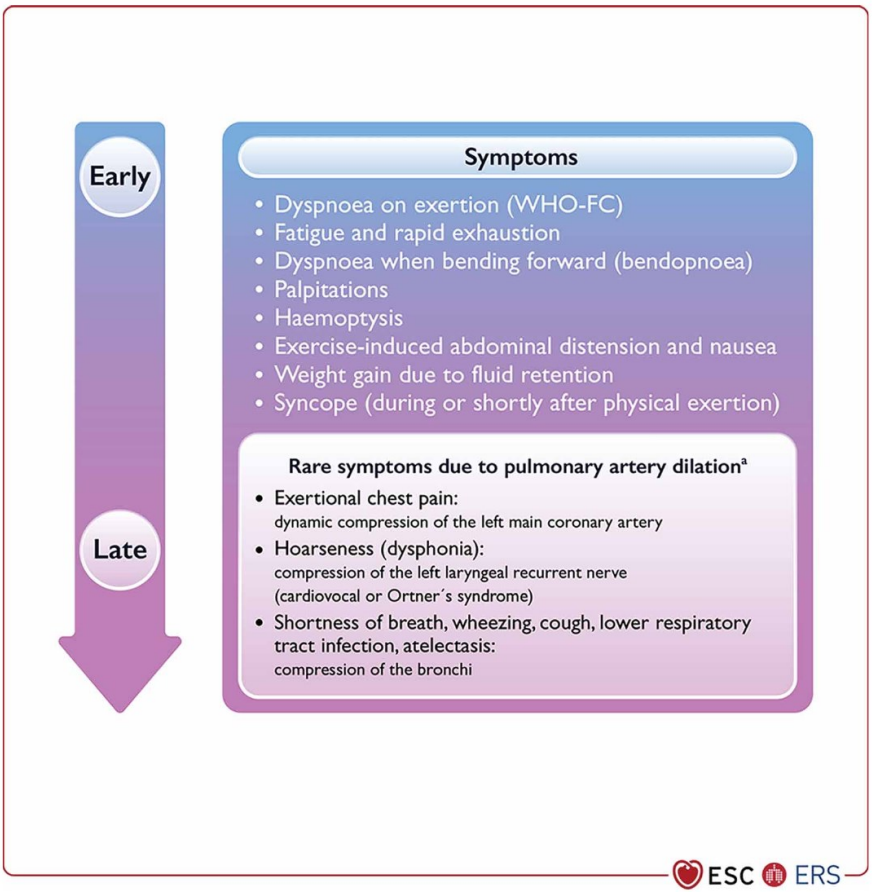


Figure 8. Symptoms of pulmonary hypertension, ordered from the early to the advanced stages of the disease.

From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

During the assessment of the patient with suspected PH, physical examination can therefore be decisive in pointing towards the underlying cause of pulmonary hypertension (25). The signs that may be found are divided into four groups (Figure 9):

- **Signs of pulmonary hypertension itself**: central, peripheral or mixed cyanosis; accentuation of the pulmonary component of the second heart sound; a third heart sound of right ventricular origin; a systolic murmur from tricuspid regurgitation; a diastolic murmur from pulmonary regurgitation (25);
- **Signs of backward right heart failure**: pulsatile jugular venous distension, abdominal distension, hepatomegaly, ascites and dependent oedema (25);
- **Signs of forward right heart failure**: peripheral cyanosis, dizziness, pallor, cold extremities and delayed capillary refill (25);
- **Signs pointing to the underlying cause**: finger clubbing, which is associated among other things with fibrosing lung disease and with bronchiectasis; lung or cardiac auscultatory findings; evidence of previous deep vein thrombosis; telangiectasia, sclerodactyly and Raynaud phenomenon in connective tissue disease (25).

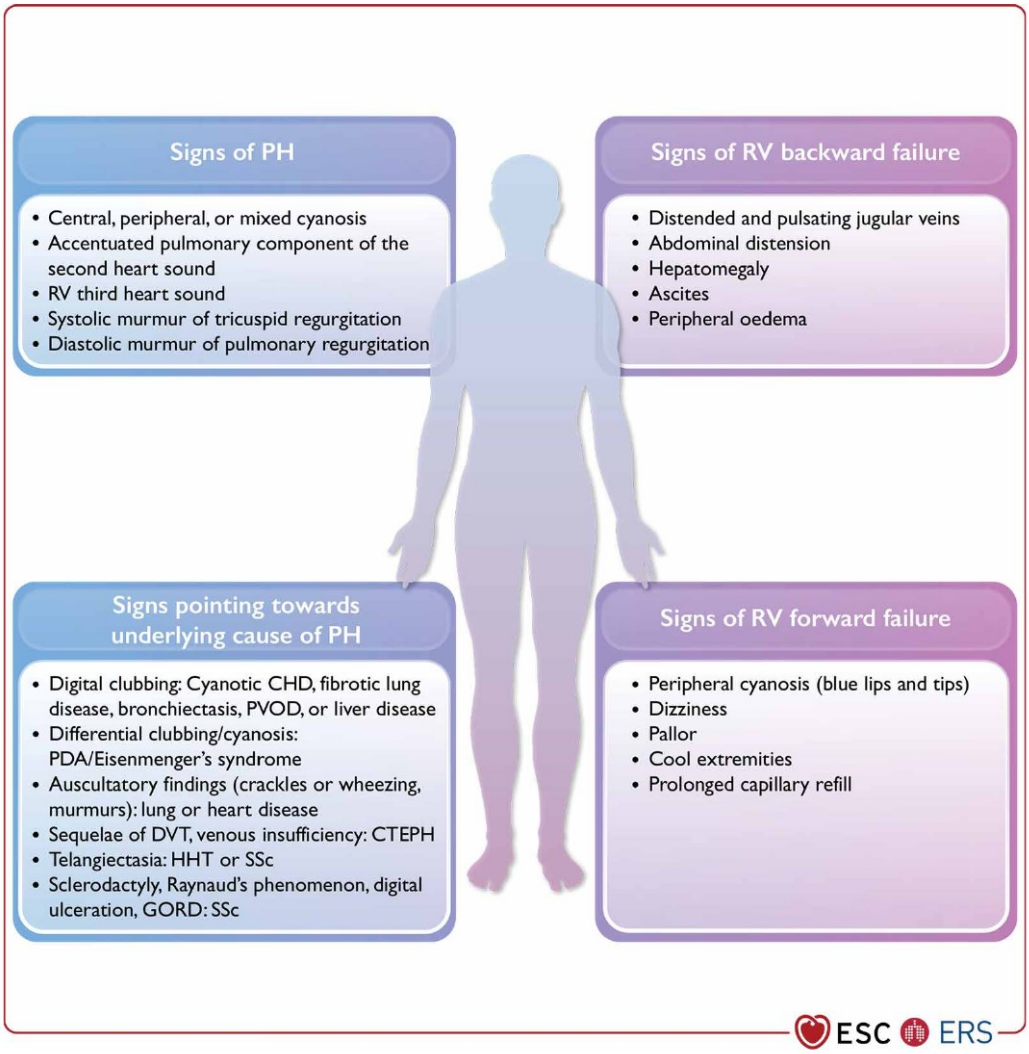


Figure 9. Clinical signs of pulmonary hypertension, divided into signs of the condition itself, signs of forward and backward right ventricular failure, and signs pointing to the underlying cause.
From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

In the patient with chronic lung disease, it is even harder to suspect pulmonary hypertension, because the overlap between the symptoms of the two conditions is almost complete: dyspnoea on exertion, the cardinal symptom of pulmonary hypertension, is also the dominant symptom of the lung disease, and the physical findings are equally non-specific (25). In idiopathic pulmonary fibrosis the problem arises in the same terms, to the point that the diagnosis of pulmonary hypertension is difficult without a high level of clinical suspicion (35).

3. PULMONARY HYPERTENSION AND THE RIGHT HEART IN IDIOPATHIC PULMONARY FIBROSIS

3.1 Definition and Epidemiology

Pulmonary hypertension is one of the most frequent complications of idiopathic pulmonary fibrosis. In the clinical classification described in the previous chapter it belongs to Group 3, among the lung diseases with a restrictive pattern, and is labelled IPF-PH (25,32,36).

The guidelines describe the third group as made up mainly of older male patients, with a frequent smoking history and a diffusing capacity for carbon monoxide that is often very low, below 45% of predicted (25).

A non-severe and a severe form are distinguished in this context as well, on the basis of haemodynamic measurements. Until 2015 the severe form was defined by a mean pressure above 35 mmHg, or by lower values combined with reduced cardiac output (25). Two later studies showed, however, that in patients with pulmonary hypertension associated with chronic obstructive pulmonary disease or with interstitial lung disease, prognosis is predicted better by vascular resistance than by pressure. The definition used today therefore adopts the value of 5 Wood units as the cut-off (25).

In epidemiological terms there is no single prevalence figure, because the estimate depends on the stage of the lung disease. The older series used a threshold of 25 mmHg of mean pressure. In those series the complication was found in 8-15% of patients with idiopathic pulmonary fibrosis at the initial assessment, in 30-50% in advanced disease and in more than 60% in the terminal phase (32). The highest estimates come from the series with haemodynamic data, which however concern selected patients, mostly transplant candidates (36–39).

The definition adopted also affects the estimate. When the progressively more inclusive criteria introduced by the World Symposia are applied in sequence to the same population with interstitial lung disease, the proportion of patients who meet them rises from 49.6% to 69.4% (39).

In most patients with idiopathic pulmonary fibrosis the form is nonetheless mild or moderate, although it can also be severe (32) (Figure 10). Progression is typically slow,

with an increase in mean pressure estimated at around 1.8 mmHg per year, but rapid progression has also been described in the advanced stages (32). Even the non-severe form has a negative effect on symptoms, on survival and on the risk of hospitalisation (25).

3.2 Pathophysiology

The rise in pulmonary pressure is not produced by a single mechanism, but by several abnormalities that act in parallel and whose main outcome is vascular remodelling (40,41).

Vascular remodelling means the structural alteration of the wall of the pulmonary vessels, in which the small arteries develop hypertrophy of the media, the arterioles become muscularised, the intima thickens through fibrosis, and pulmonary vascular resistance rises in a stable way (40,41). In idiopathic pulmonary fibrosis a similar constrictive thickening has also been described in the pulmonary veins, both in fibrotic areas and in areas with preserved architecture, and even in the absence of arterial remodelling, so that the process involves the whole vascular bed and not the arteries alone (40).

The first determinant is alveolar hypoxia. In the healthy lung a fall in alveolar oxygen tension causes local vasoconstriction, which diverts flow away from poorly ventilated areas (40). In idiopathic pulmonary fibrosis hypoxia involves extensive areas and does not resolve, so that vasoconstriction becomes generalised and loses its compensatory function (40).

When the stimulus persists, the structural alteration of the wall is added over time to vasoconstriction and turns a reversible functional response into stable remodelling (40,41).

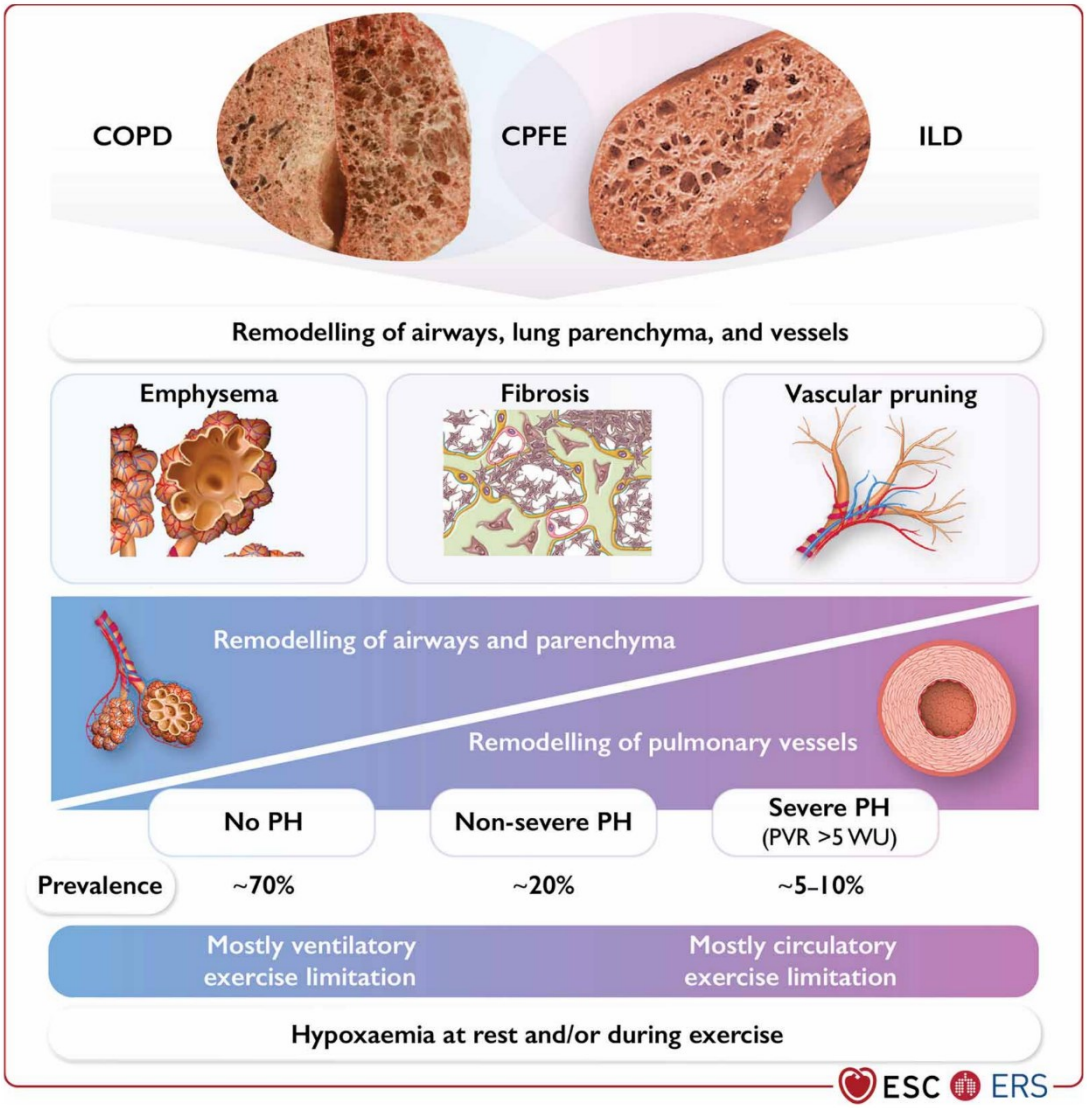


Figure 10. Pulmonary hypertension associated with lung disease.
The upper panel shows the underlying lung diseases; the middle panel shows the abnormalities of airways, parenchyma and vessels that contribute to it; the lower panel shows the distribution of patients between absence of pulmonary hypertension, non-severe form and severe form, with the type of exercise limitation that follows. From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

Alongside these mechanisms there is also endothelial alteration, which contributes to the proliferative component of remodelling (42). In pulmonary hypertension the physiological balance between vasodilator and vasoconstrictor mediators is lost, because the synthesis of nitric oxide and prostacyclin falls while that of endothelin-1 rises, and the expression of endothelin-1 correlates with pulmonary vascular resistance

(42). What triggers this alteration is not known, but alveolar hypoxia itself, the increase in the shear forces exerted by blood on the vessel wall when flow rises, and some viral infections acting in genetically predisposed subjects all appear to be involved (42).

The result is a higher vascular tone, a pro-thrombotic state and the loss of barrier function, which leaves the wall exposed to circulating growth factors (42). The expression of these factors is in turn regulated by the hypoxia-inducible factor HIF-1α, which rises under hypoxic conditions and induces the production of VEGF and PDGF-β, with consequent proliferation of smooth muscle cells and fibroblasts (40,43,44).

Cigarette smoke acts on the same pathways and, in idiopathic pulmonary fibrosis, is the environmental factor most consistently associated with the disease, as set out in Chapter 1. It reduces the expression of endothelial nitric oxide synthase, increases that of VEGF and produces intimal hyperplasia, inflammatory cell infiltration and mitochondrial oxidative stress (40).

An individual predisposition is also suggested by the gene expression profile. In patients with idiopathic pulmonary fibrosis and pulmonary hypertension, the mediators of smooth muscle cell and endothelial proliferation are overexpressed (40).

In addition, IPF also involves the anatomical loss of part of the vascular bed, since the destruction of the alveolar septa removes microvessels and capillaries from the pulmonary circulation and reduces the vessels available to flow (40,41). In advanced disease, dense fibrosis also compresses both peripheral and central vessels (40).

Histologically, therefore, arterial remodelling and a reduced capillary density are seen in the fibrotic areas, whereas in the areas with preserved architecture capillary density is highest and the arteries keep a thin wall (40) (Figure 11).

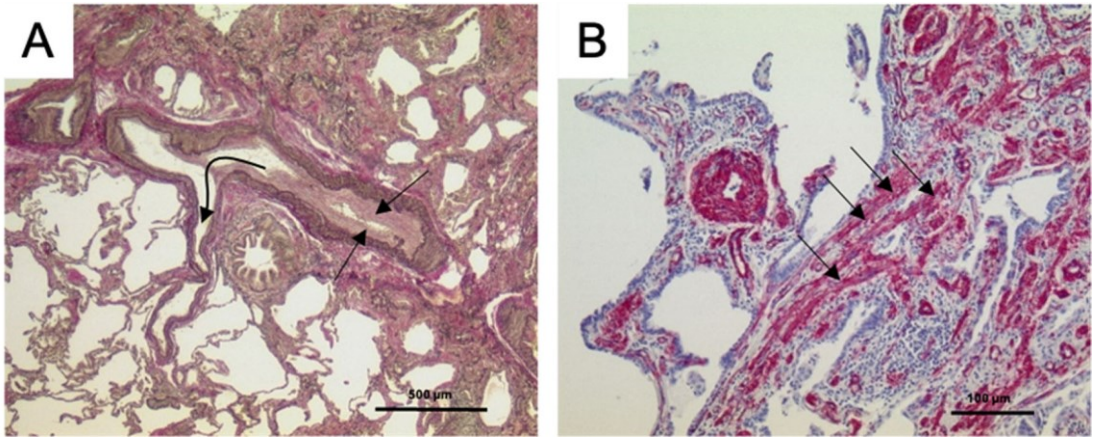


Figure 11. Pulmonary vascular changes in the patient with idiopathic pulmonary fibrosis and pulmonary hypertension.

A: constrictive intimal fibrosis of a pulmonary artery within the fibrotic area (straight arrows), compared with the thin wall of the arterial branch supplying the areas with preserved architecture (curved arrow). B: smooth muscle cell hyperplasia in the interstitium and in the wall of a small pulmonary artery (arrows). Panels A and B of the original figure. From: Singh N, et al. Group 3 Pulmonary Hypertension: From Bench to Bedside. Circ Res 2022;130(9):1404-1422 (40).

Finally, parenchymal and vascular remodelling have been shown to progress independently of each other, and the degree of parenchymal involvement does not correlate with the severity of pulmonary hypertension (40).

3.3 The Right Ventricle in Pulmonary Hypertension

Pulmonary hypertension imposes an increase in afterload on the right ventricle, and this is the mechanism that links lung disease to right heart dysfunction (40). The greater work required produces hypertrophy and dilatation, which may progress to ventricular dysfunction (41), and among the determinants of the course and of prognosis the function of the right ventricle holds a leading position (45,46). The right chamber is particularly vulnerable to this increase in load, because its wall is thin and, for the same rise in pressure, the resulting wall stress is greater than in the left ventricle (46).

3.3.1 From Adaptation to Failure

Right ventricular failure is defined as the clinical syndrome in which the function of the right ventricle is reduced to the point of producing insufficient blood flow, high filling pressures, or both, at rest or during physical effort (45).

The first response to an increase in load is a rise in contractility, accompanied by hypertrophy of the wall (45). The ventricle generates more force while keeping its own

dimensions and stroke volume unchanged. In pulmonary arterial hypertension contractility can increase up to fivefold (45). As long as this increase remains proportionate to the load, ventricle and pulmonary circulation stay coupled and function appears preserved at rest (45).

What is lost first is therefore not performance at rest, but contractile reserve, that is the ability to increase contractility further when demand rises (45). In the normal ventricle contractility rises significantly during exercise, whereas in the overloaded ventricle this increase is smaller and in advanced disease it is absent (45). The ratio between contractility and load falls gradually from the early stages, while clear uncoupling, the one accompanied by dilatation of the ventricle, becomes apparent at rest only late (45).

When contractile adaptation is no longer sufficient the ventricle dilates instead, and at this point end-diastolic volume rises, stroke volume falls and filling pressures increase (45). The speed of this evolution is determined by the increase in wall stress, by neurohormonal activation, by oxidative stress, by inflammation, by myocardial ischaemia and cell death, as well as by the acute or chronic course of the disease and by the age at which the process begins (47,48). Myocardial remodelling can thus take on an adaptive character, in which coupling remains only slightly altered, or a maladaptive one, which leads to dilatation, failure and arrhythmias (46) (Figure 12).

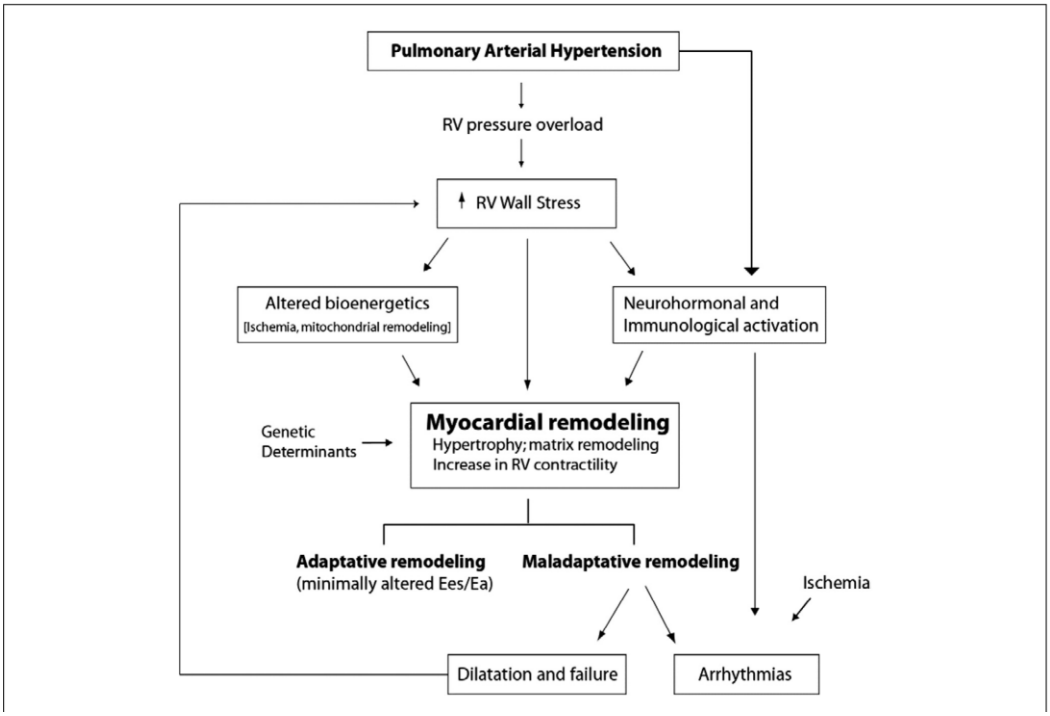


Figure 12. Pathophysiology of right ventricular dysfunction in pulmonary arterial hypertension. The increase in afterload produces a rise in wall stress, alongside neurohormonal and immune activation and altered cellular bioenergetics. Myocardial remodelling follows, and it may be adaptive, with only slightly altered Ees/Ea coupling, or maladaptive, leading to dilatation, failure and arrhythmias. From: Vonk-Noordegraaf A, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol 2013;62(25 Suppl):D22-D33 (46).

3.3.2 The Right Ventricle in Chronic Lung Disease

In chronic lung disease the increase in vascular resistance is typically slow, and the right ventricle therefore has the time it needs to compensate (40). The result is hypertrophy with preserved systolic function, in which the prevailing abnormality is diastolic (40). The ventricle therefore stays in the compensated phase for a long time, and in this phase the systolic function parameters in common use are normal (40).

The deterioration of right ventricular function is moreover largely a functional and not a structural phenomenon, and in this the right chamber behaves differently from the left one (46). When the left ventricle is exposed to chronic pressure overload, as in aortic stenosis or in systemic arterial hypertension, the myocardium undergoes extensive and therefore irreversible fibrous replacement (46). In the right ventricle fibrosis remains limited, often below 10% of ventricular volume and largely confined to the septal insertion points (49). This is the reason why, as documented in several series, most patients with severe right heart failure recover ventricular function after

lung transplantation, even when right ventricular ejection fraction is severely reduced at the time of surgery (46).

The two ventricles finally share the interventricular septum, some myocardial fibres and the pericardial sac, and influence each other (45). In pulmonary hypertension the myocytes exposed to mechanical stress lengthen their contraction time and the free wall of the right ventricle contracts for longer than the septum (46). When the left ventricle is already in early diastole the septum is pushed to the left, and from this asynchrony it follows that part of the right-sided contraction is ineffective while the filling of the left ventricle is reduced (45,46).

3.4 Clinical Suspicion and Diagnostic Delay

Recognition of the vascular complication in idiopathic pulmonary fibrosis is made difficult by three circumstances that add to one another: the severity of the vascular disease cannot be inferred from that of the parenchymal disease, the symptoms of the two conditions coincide, and no planned surveillance is provided.

The first circumstance is documented by haemodynamic data. The correlation between forced vital capacity and pulmonary vascular resistance is very weak, and more than half of the patients with a diffusing capacity equal to or above 40% of predicted still have a resistance above 3 Wood units (39). In the registry of transplant candidates, pulmonary pressure is not distributed according to forced vital capacity or forced expiratory volume in one second but is associated with oxygen requirement and with wedge pressure (38). The severity of the ventilatory defect therefore does not predict, in the individual patient, the severity of the vascular disease (40).

The second circumstance is the clinical overlap, already described in the previous chapter. Exertional dyspnoea is the cardinal symptom of both conditions, and the physical findings are non-specific, to the point that, in idiopathic pulmonary fibrosis, the diagnosis of pulmonary hypertension is difficult without a high level of clinical suspicion (25,35). Suspicion cannot therefore rest on the appearance of new symptoms, but rather on their disproportion to the degree of documented respiratory impairment, on the appearance of signs of right heart failure and on a clinical deterioration that is not matched by functional decline (36). In its extreme form this disproportion defines

the pulmonary vascular phenotype, with preserved spirometry, disproportionately reduced diffusing capacity, hypoxaemia and exercise limitation of a circulatory rather than ventilatory type (25).

The third circumstance is the absence of screening. In the patient with lung disease the guidelines recommend echocardiography only when pulmonary hypertension is already suspected, and their diagnostic algorithm does not include any surveillance pathway for the groups at risk (25).

The result is late recognition, documented in clinical practice. In one referral centre, right heart catheterisation was performed in 12.2% of the patients with interstitial lung disease followed over eighteen years, and almost a third of them already had a severe form at the time of the examination(39).

3.5 Diagnostic Work-Up

The diagnostic work-up is organised in three levels. The first-level investigation is echocardiography, which is non-invasive, repeatable and able to identify alternative causes such as left heart disease, which is particularly common in the patient with chronic lung disease (40). It should be performed when the patient is clinically stable, because exacerbations raise pulmonary pressure considerably and its results should be read together with arterial blood gases, pulmonary function tests and computed tomography (25).

Alongside it there are complementary investigations, which do not by themselves allow a diagnosis but change the probability of disease and help to exclude other causes. The guidelines recommend interpreting them together and not as alternatives to one another (25). The third level is right heart catheterisation, which remains the only confirmatory test (40).

3.5.1 Echocardiography: Pressure Estimation and the Probability of Pulmonary Hypertension

The examination addresses the question in two distinct and complementary ways. The first is the estimate of systolic pulmonary artery pressure (PAPs), the second is the recognition of the indirect signs of right ventricular overload(25).

The pressure estimate starts from tricuspid regurgitation, the backflow of blood that crosses the tricuspid valve during systole, from the right ventricle towards the right atrium. What the examination measures is the peak velocity of this jet, and a technically adequate signal can be obtained in the majority of patients (50). Since the measurement of velocity depends on the angle between the ultrasound beam and the direction of flow, the signal is gathered from several acoustic windows and the one with the highest velocity is used (50).

From this velocity the systolic pressure of the right ventricle is derived. The simplified Bernoulli equation converts the peak velocity into the systolic pressure gradient between the right ventricle and the right atrium, known as the transtricuspid gradient, and right atrial pressure is then added to it, according to the relationship PAPs = $4V^2$ + RAP (50). In the absence of a gradient across the pulmonary valve or the right ventricular outflow tract, systolic pulmonary artery pressure is equal to right ventricular systolic pressure, and the two are therefore used as synonyms (50).

Right atrial pressure, however, is not measured. It is estimated from the diameter of the inferior vena cava and from its inspiratory collapse, and to each of the three possible combinations a conventional value of 3, 8 or 15 mmHg is assigned (50).

The estimated systolic pulmonary artery pressure therefore rests on a value that is assigned by convention rather than measured. Considering the inaccuracy in estimating right atrial pressure and the amplification of measurement error that comes from using a derived variable, the guidelines recommend the peak velocity of tricuspid regurgitation, and not the estimated systolic pressure, as the key variable for assigning the echocardiographic probability of pulmonary hypertension (25). A peak velocity above 2.8 m/s may suggest pulmonary hypertension, but the presence or absence of the condition cannot be reliably determined by the velocity alone (25). The velocity may moreover underestimate the gradient, as in severe tricuspid regurgitation, or overestimate it, as when cardiac output is high (25).

Alongside the velocity of the regurgitation there are additional echocardiographic signs, which the guidelines divide into three categories (25):

- ventricular signs: a ratio between the basal right and left diameters above 1.0, flattening of the interventricular septum with a left ventricular eccentricity index above 1.1, a TAPSE/PAPs ratio below 0.55 mm/mmHg;
- pulmonary artery signs: an acceleration time in the right ventricular outflow tract below 105 ms or mid-systolic notching, an early diastolic pulmonary regurgitation velocity above 2.2 m/s, a pulmonary artery diameter larger than that of the aortic root or in any case above 25 mm;
- signs of the inferior vena cava and right atrium: a caval diameter above 21 mm with reduced inspiratory collapse, an end-systolic right atrial area above 18 cm^2.

For the probability of pulmonary hypertension to change, signs from at least two categories must be present (25). Combining the velocity of the regurgitant jet with the additional signs gives a low, intermediate or high echocardiographic probability, and the guidelines link a recommended course of action to each of them (25) (Figure 13):

- low probability, for a velocity equal to or below 2.8 m/s or not measurable in the absence of additional signs: an alternative diagnosis is sought;
- intermediate probability, for the same velocity in the presence of additional signs or for a velocity between 2.9 and 3.4 m/s without additional signs: echocardiographic follow-up over time is indicated;
- high probability, for a velocity above 3.4 m/s or between 2.9 and 3.4 m/s with additional signs: further investigations and, when appropriate, right heart catheterisation are indicated.

The guidelines specify, however, that catheterisation should be performed only when its results are expected to be useful for management decisions, which include referral to a specialist centre and assessment for transplantation as well as the choice of treatment, and that it may not be indicated in the presence of mild pulmonary hypertension with predominant lung disease (25).

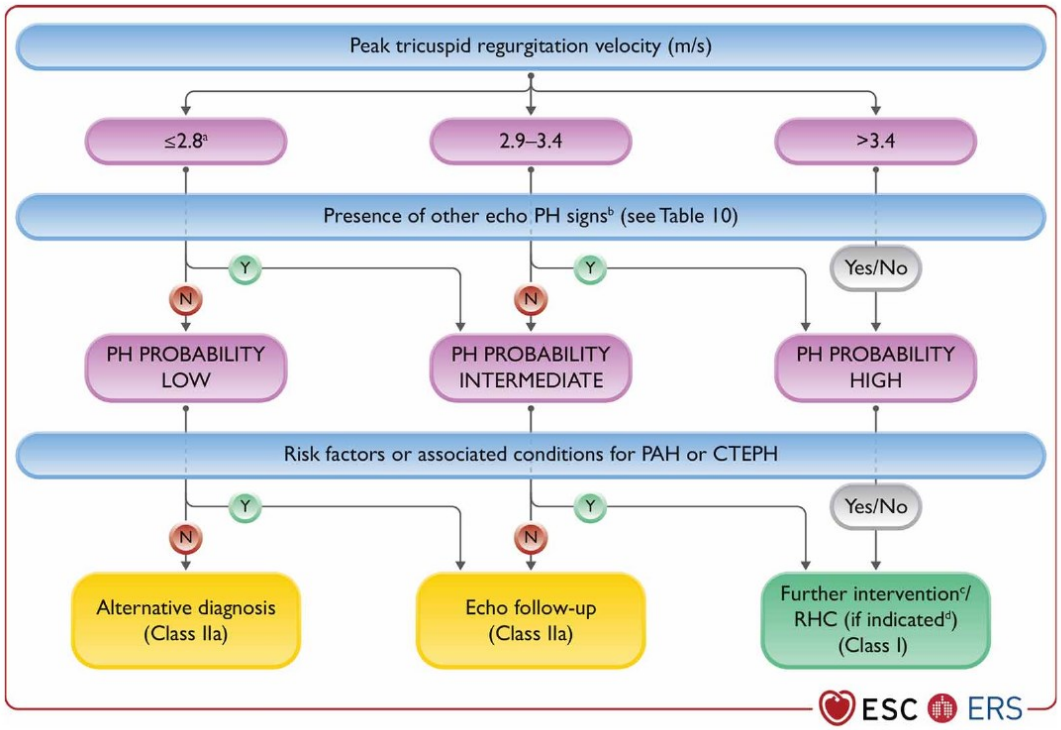


Figure 13. Echocardiographic probability of pulmonary hypertension and recommended course of action.

The level of probability is obtained by combining the peak velocity of tricuspid regurgitation with the presence of additional echocardiographic signs from at least two of the three categories. RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

3.5.2 Echocardiography: The Parameters of Right Ventricular Function

Echocardiographic probability concerns the presence of pulmonary hypertension and not the state of the right ventricle, whose function nonetheless determines the course and the prognosis (45,46). The examination therefore includes a set of dedicated parameters, which measure different aspects of function and are not interchangeable with one another (50).

TAPSE (tricuspid annular plane systolic excursion) measures how far the plane of the annulus travels during systole, that is the longitudinal shortening of the right ventricle and is acquired by placing the M-mode cursor through the annulus in the apical four-chamber view (50). It is the most widely used parameter, because it is easy to perform and reproducible, but it assesses only the longitudinal component and assumes that the movement of a single segment represents the whole ventricle. Values

below 16 mm indicate systolic dysfunction, without however saying how severe it is (50).

The S' wave expresses how fast that same annulus moves during systole and is measured by pulsed tissue Doppler, and values below 10 cm/s indicate dysfunction (50). Although they refer to the same anatomical point, TAPSE and the S' wave describe different things, one the distance travelled and the other the speed, and they are therefore not interchangeable (51).

Fractional area change instead estimates the global function of the chamber and is calculated as the difference between end-diastolic and end-systolic area, divided by the end-diastolic area (50). Because it also takes the radial component into account, it correlates with right ventricular ejection fraction measured by magnetic resonance imaging, and values below 35% are considered abnormal (50). The assessment is completed by the dimensions of the right chambers, which are abnormal above 4.2 cm for the basal ventricular diameter and above 18 cm^2 for the end-systolic right atrial area (50,52).

All the parameters described so far follow the movement of a point or the change in an area, whereas myocardial strain measures how much the wall itself deforms, that is the percentage change in length that each segment undergoes during systole compared with its own initial length. It is obtained from the same echocardiogram with the speckle tracking technique, which follows the natural acoustic markers of the myocardium frame by frame (53). Since this shortening is expressed as a negative number, reduced deformation corresponds to a less negative value, that is to a wall that shortens less, and it therefore indicates worse function (53).

The value of strain lies in having shown the limits of the displacement parameters. When normal subjects, patients with compensated right ventricular function and patients with decompensated right ventricular function are compared, free wall strain is already reduced in the compensated phase, when the conventional parameters are still normal (54). In a meta-analysis, the risk of death associated with a strain value beyond the threshold is more than tripled, whereas for TAPSE the same association does not reach statistical significance (55). A normal longitudinal movement can therefore coexist with a wall that already deforms less than it should, and a TAPSE

within the normal range does not exclude right ventricular dysfunction (56). The parameters described in this section are illustrated in Figure 14.

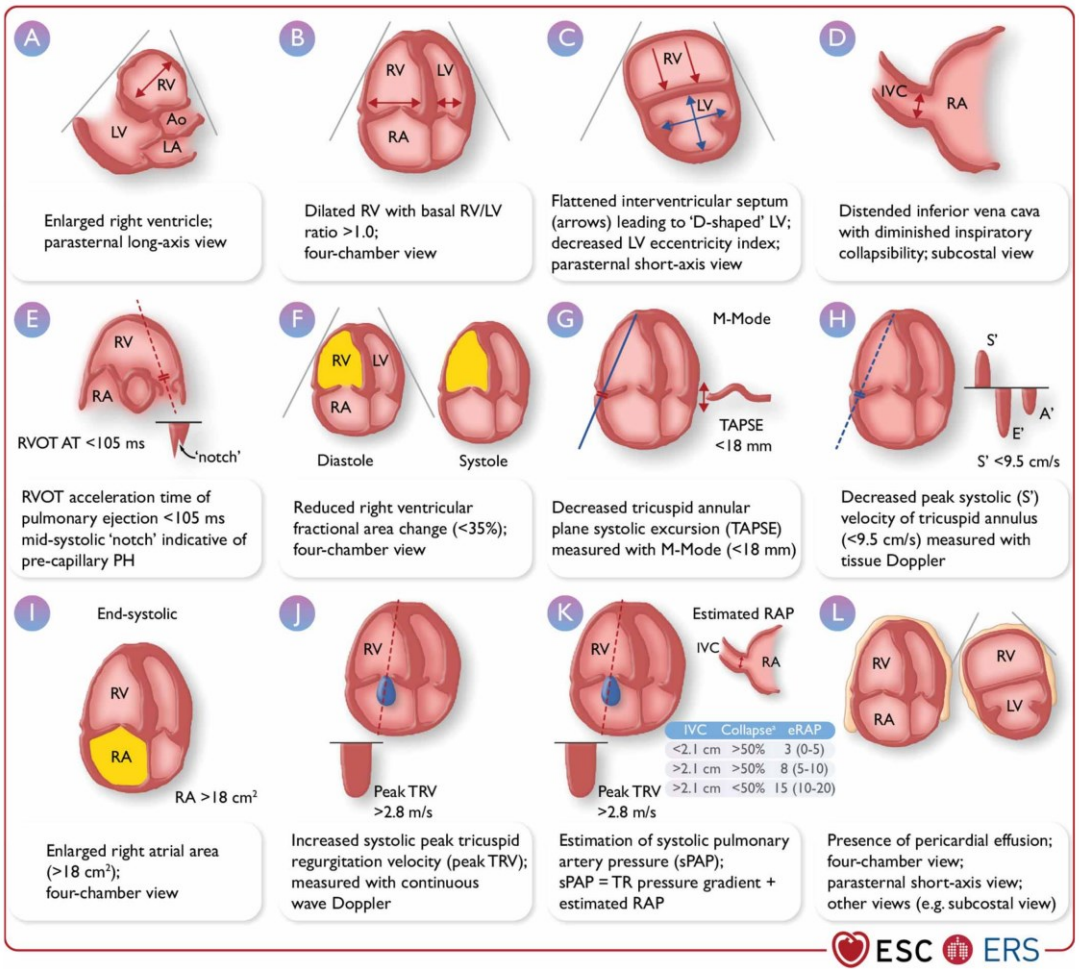


Figure 14. Transthoracic echocardiographic parameters in the assessment of pulmonary hypertension.

A and B: enlargement and dilatation of the right ventricle. C: flattening of the interventricular septum. D: dilated inferior vena cava with reduced inspiratory collapsibility. E: reduced acceleration time in the right ventricular outflow tract with mid-systolic notching. F, G and H: reduction of fractional area change, of TAPSE and of the systolic velocity of the tricuspid annulus. I: increased right atrial area. J and K: peak velocity of tricuspid regurgitation and estimation of systolic pulmonary artery pressure. L: pericardial effusion. From: Humbert M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1):2200879 (25).

The function of the right ventricle is of particular importance in Group 3, which includes the interstitial lung diseases. For the same mean pulmonary pressure, patients in this group have a lower fractional area change than those in Group 1, and the difference persists after adjustment for age, sex and comorbidities (57). Right ventricular dysfunction in Group 3 is therefore disproportionate to the haemodynamic severity, so that pressure data alone cannot account for it (57) (Figure 15).

The response to afterload also differs between the sexes, since in Group 3 men have worse right ventricular systolic function than women, even though women have higher vascular resistance. Sex must therefore be considered when interpreting an index of right ventricular function (40).

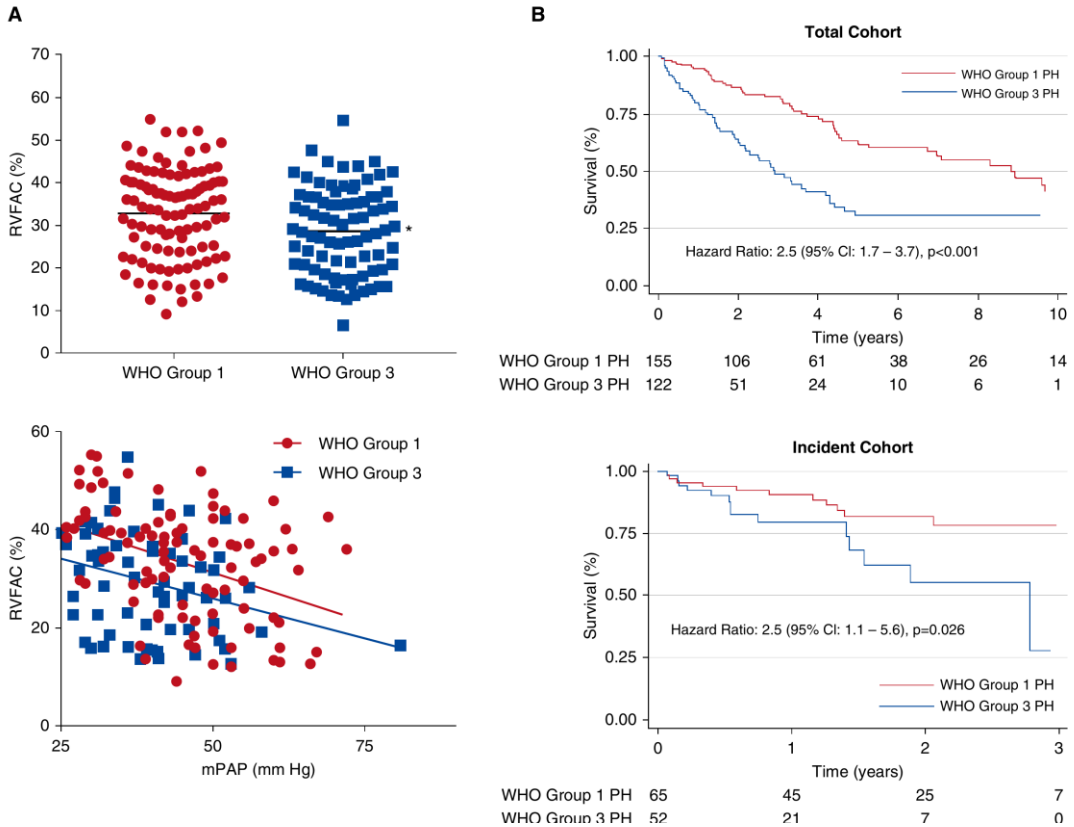


Figure 15. Right ventricular function and mortality in Group 3 pulmonary hypertension.
A: right ventricular fractional area change in Group 3 compared with Group 1 (28 ± 10% versus 33 ± 11%) and its relationship with mean pulmonary artery pressure; the slope of the regression lines is similar in the two groups, whereas the intercept is significantly lower in Group 3. B: survival curves. From: Prins KW, et al. Disproportionate Right Ventricular Dysfunction and Poor Survival in Group 3 Pulmonary Hypertension. Am J Respir Crit Care Med 2018;197(11):1496-1499 (57).

In idiopathic pulmonary fibrosis the difference between displacement parameters and deformation parameters emerges already in the early stages. In the initial stages of the disease right ventricular diameters are slightly increased, whereas TAPSE, the S' wave and right ventricular stroke volume are similar to those of healthy controls; global longitudinal strain and free wall strain are instead significantly reduced (58).

During exercise the same patients show a greater rise in systolic pulmonary pressure and a smaller rise in free wall strain, which expresses a reduced contractile reserve of the right ventricle (58).

The same finding is repeated in non-severe idiopathic pulmonary fibrosis, defined by the authors of the study as the absence of hypoxaemia at rest and a GAP index no higher than 5 (59). In this population, strain measured with speckle tracking identifies right ventricular dysfunction in more than a third of the patients, while none of them shows abnormalities of the conventional parameters (59). The patients with dysfunction also have a higher estimated mean pulmonary pressure both at rest and at peak exercise, and the difference persists even when the analysis is limited to those with normal systolic pressure at rest, so that the dysfunction is not simply the consequence of already established pulmonary hypertension (59).

3.5.3 The Limits of Echocardiography in Advanced Lung Disease

In advanced respiratory disease the accuracy of echocardiography in estimating pulmonary pressure is low (25). The documented limits concern the possibility of obtaining the measurement, its accuracy and its repeatability over time.

The first limit is measurability. Hyperinflation and distortion of the parenchyma worsen the acoustic window, and the guidelines report that in some series of advanced respiratory disease the velocity of tricuspid regurgitation cannot be measured in more than half of the patients (25). In lung transplant candidates the estimate of systolic pressure could be obtained in fewer than half of the cases overall and in slightly more than half of the subgroup with interstitial lung disease (60), while even in a centre dedicated to pulmonary hypertension 5.4% of the examinations are unusable because of a poor acoustic window or an inadequate regurgitation signal (61).

The second limit is the accuracy of the measurement when it can be obtained. In lung transplant candidates the estimate of systolic pressure differs by more than 10 mmHg from the invasive value in about half of the cases, and almost half of the patients with a high estimate turn out not to have pulmonary hypertension at catheterisation (60). The direct comparison between mean pressure measured at catheterisation and mean pressure calculated from echocardiography shows a negligible mean error, equal to -2 mmHg, but a wide scatter, with single measurements differing from the true value by up to 11 mmHg above and 15 mmHg below (61). The method is therefore reliable for the mean value of a population and imprecise for the individual patient. The limit moreover weighs most heavily on the patients this work is concerned with, because in

obstructive disease a negative examination makes the condition unlikely, whereas in the subgroup with interstitial lung disease the negative predictive value is clearly lower and a negative examination is not enough to exclude it (60).

The third limit concerns monitoring over time. In the REVEAL registry the correlation between estimated and measured pressure is good at baseline, whereas serial measurements show poor correlation, and echocardiography alone is therefore not sufficient to follow the course of pressure (62).

These limits do not, however, justify disregarding modest rises in pressure. Patients with an estimated systolic pulmonary artery pressure between 33 and 39 mmHg have almost twice the prevalence of ventricular dysfunction compared with those with lower values, and the increase in adjusted mortality begins as early as 27 mmHg (63).

3.5.4 Complementary Investigations

Among the investigations that accompany echocardiography, the electrocardiogram and biomarkers have a limited role. Right axis deviation has a positive predictive value of 93% for pulmonary hypertension (25,64), but in chronic lung disease the electrocardiographic recognition of right ventricular hypertrophy has very low sensitivity and a normal tracing does not exclude the condition (41). Among circulating biomarkers, natriuretic peptide is the most accurate, but its specificity is low and the result may be confounded by coexisting left heart disease (40,65).

On computed tomography, dilatation of the pulmonary artery reflects chronic exposure to high pressures and is among the indirect signs considered by the guidelines (25,66). In the patient with idiopathic pulmonary fibrosis, however, the pulmonary artery may be dilated even in the absence of pulmonary hypertension as an effect of the fibrosis, and the sign considered in isolation is therefore unreliable (36).

Diffusing capacity for carbon monoxide also contributes to the suspicion. A reduction that is disproportionate to the ventilatory defect is associated with the presence of the vascular complication and with shorter survival (40), and the parameter keeps its prognostic value even among patients with a similar haemodynamic profile (49,67).

3.5.5 Right Heart Catheterisation

Right heart catheterisation remains the confirmatory test and in Group 3 it serves two purposes. The first is to distinguish the pre-capillary from the post-capillary profile, that is to establish whether the overload depends on the pulmonary circulation or on left-sided filling pressures (25). The second is to define the severity of the condition, which, as has been seen, is based on pulmonary vascular resistance (40).

In the patient with interstitial lung disease the indications for catheterisation include clinical worsening that is disproportionate to the ventilatory defect, assessment for lung transplantation and the start of specific treatment (40). The safety profile of the procedure is favourable, since across more than seven thousand examinations performed in experienced centres serious adverse events occurred in just over 1% of the cases, with a related mortality below one case in a thousand (68).

Assignment to Group 3 is finally based on the consistency between the extent of the ventilatory defect, the CT findings and the degree of pulmonary hypertension, which in the forms associated with lung disease is usually mild to moderate (32).

3.6 Ventricular-Arterial Coupling

3.6.1 Definition and Measurement

The parameters described in the previous section measure the function of the right ventricle without taking account of the load against which that function is exerted. Right heart failure is not, however, the expression of a primary myocardial disease, but of the load imposed by the pulmonary circulation, and its study therefore requires the cardiopulmonary unit to be considered as a whole, that is the ventricle together with the vascular bed that loads it (45).

Ventricular-arterial coupling arises from this need, because it describes the efficiency with which the ventricle transfers energy to the circulation that loads it and is the physiologically most correct way of relating contractility and afterload (45). It is expressed as the ratio between the end-systolic elastance of the ventricle (Ees), which measures contractility independently of load, and arterial elastance (Ea), which measures the load itself. Energy transfer is maximal for values between 1.5 and 2,

which correspond to the best balance between mechanical work produced and oxygen consumed(46,69).

The system also has a considerable reserve, since the ratio has to fall to about 0.8 before right ventricular volume exceeds the normal limit and failure becomes clinically recognisable (69,70). It is in this reserve that the clinical interest of the measurement lies, since in principle it allows the deterioration of coupling to be detected while the ventricle still appears compensated (69,70).

Direct measurement remains, however, difficult to carry out. End-systolic elastance is obtained from the analysis of the pressure-volume curves of the right ventricle, ideally recorded while ventricular filling is reduced by partial occlusion of the vena cava. Even in the simplified single-beat versions the method remains invasive, technically demanding and impossible to perform at the bedside (45,70). It is from this difficulty that the search for non-invasive surrogates arises, that is for measurements obtainable with echocardiography that behave in a way like the ratio between elastances (70). The curves and their meaning are illustrated in Figure 16.

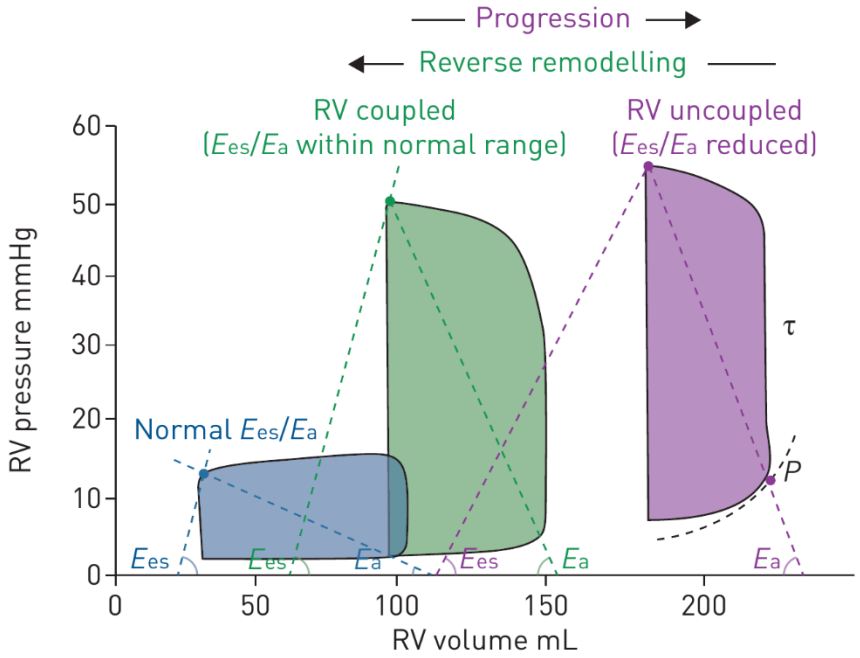


Figure 16. Pressure-volume analysis of the right ventricle.

Curves at three different stages: normal (in blue), pulmonary hypertension with a coupled ventricle (in green, Ees/Ea ratio within the normal limit) and right ventricular failure with an uncoupled ventricle (in purple, reduced Ees/Ea ratio). Ees: end-systolic elastance; Ea: arterial elastance; τ: time constant of ventricular relaxation. From: Vonk Noordegraaf A, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53(1):1801900 (45).

3.6.2 The TAPSE/PAPs Ratio

The ratio between TAPSE and systolic pulmonary artery pressure was proposed by Guazzi and co-workers in heart failure, with the aim of representing in echocardiographic form the length-force relationship of the right ventricle: TAPSE measures its shortening, systolic pressure the force generated against the load (71). Already in that setting the ratio showed greater prognostic power than either of its two components taken alone (71).

Validation against the invasive reference came later, in patients with pulmonary arterial hypertension and with severe chronic thromboembolic pulmonary hypertension, in whom pressure-volume curves were recorded directly (70)]. When the different surrogates proposed in the literature were compared with those curves, only the TAPSE/PAPs ratio was confirmed as an independent predictor of the ratio between elastances, and a value below 0.31 mm/mmHg identifies uncoupling, with a worse prognosis below that threshold (70). The ratio is moreover also affected by the diastolic stiffness of the ventricle, and it therefore does not reflect the systolic component alone (70). In pulmonary arterial hypertension it keeps an independent association with mortality in all multivariable models (72).

The recommendations of the American Society of Echocardiography report consensus values that are not stratified by age: in healthy subjects the ratio is generally between 0.5 and 0.7 mm/mmHg, whereas in pulmonary hypertension a value between 0.3 and 0.4 mm/mmHg is associated with uncoupling and with an increased risk of death (56). The same recommendations point out that the ratio varies with age, with sex and with the method used. The ESC/ERS guidelines include it among the suggestive echocardiographic signs, with a threshold of 0.55 mm/mmHg (25).

3.6.3 Coupling in Chronic Lung Disease and in Fibrosing Interstitial Lung Disease

In pulmonary hypertension due to chronic lung disease the TAPSE/PAPs ratio distinguishes the severe from the non-severe forms with a threshold of 0.26 mm/mmHg, performs better than TAPSE and systolic pressure taken separately, and predicts survival both in the form due to chronic obstructive pulmonary disease and in that due to interstitial lung disease (69). In patients with interstitial lung disease,

moreover, neither total lung capacity nor vital capacity correlates with the ratio, and the information it carries is therefore not deducible from pulmonary function (69) (Figure 17).

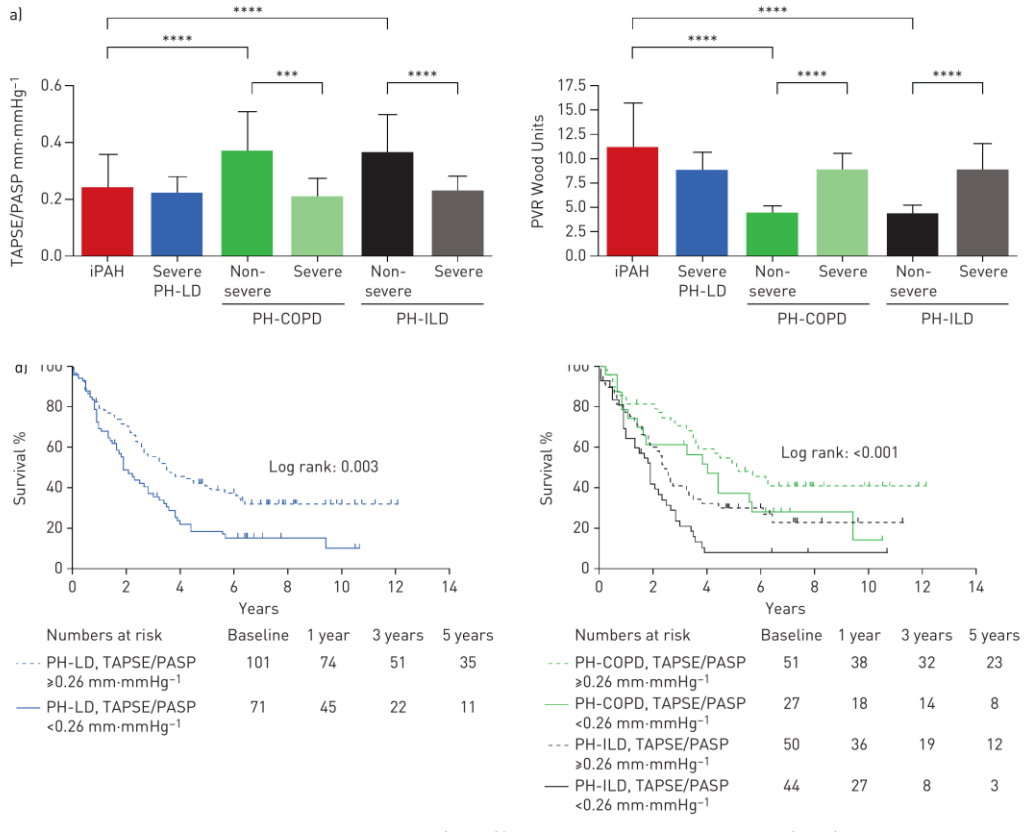


Figure 17. The TAPSE/PAPs ratio in pulmonary hypertension secondary to chronic lung disease. Above: TAPSE/PAPs ratio and pulmonary vascular resistance in patients with idiopathic pulmonary arterial hypertension and in those with pulmonary hypertension due to chronic obstructive pulmonary disease or to interstitial lung disease, stratified by haemodynamic severity. Below: survival curves stratified according to the threshold of 0.26 mm/mmHg. Panels a and d of the original figure. From: Tello K, et al. A simple echocardiographic estimate of right ventricular-arterial coupling to assess severity and outcome in pulmonary hypertension on chronic lung disease. Eur Respir J 2019;54(3):1802435 (69).

In a series of fibrosing interstitial lung diseases, made up for slightly more than half of patients with idiopathic pulmonary fibrosis and compared with healthy controls of the same age and sex, TAPSE does not differ between the two groups whereas both coupling indices are significantly reduced (73).

In the same series, however, only the ratio built on strain is confirmed as an independent predictor of outcome, while TAPSE/PAPs does not reach prognostic significance (73). That series included fifty patients. The TAPSE/PAPs ratio remains, on the other hand, the only surrogate validated against the invasive reference

measurement (70), the only one included among the signs considered by the guidelines (25) and the only one obtainable from a routine echocardiogram, since strain requires dedicated software and images of adequate quality (53). It is this availability that makes it usable in everyday practice, while its prognostic value in fibrosing interstitial lung disease awaits confirmation in larger series (69,73). None of the thresholds reported above was derived in a population with idiopathic pulmonary fibrosis (25).

3.6.4 The Effect of Age

The thresholds reported so far are single values, applied without distinction to all ages, whereas both pulmonary pressure and the TAPSE/PAPs ratio change over the course of life even in healthy subjects (74,75).

In the healthy population, examined from childhood to old age, systolic pulmonary pressure rises while TAPSE and the TAPSE/PAPs ratio fall, and the size of the phenomenon is considerable, since the ratio goes from values around 1.3 mm/mmHg in the third decade to about 0.9 beyond the age of seventy-five (75) (Figure 18).

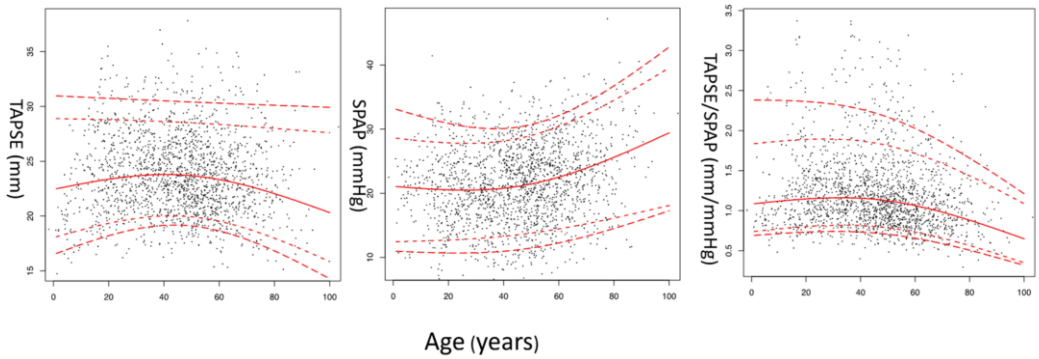


Figure 18. Changes in TAPSE, systolic pulmonary artery pressure and the TAPSE/PAPs ratio as a function of age in 1,899 healthy subjects aged between 1 and 102 years; the red lines represent the quantile regression curves.

TAPSE reaches a maximum in the third to fourth decade and declines slowly in old age, systolic pressure remains stable until the fifth decade and then rises, and the ratio between the two falls progressively. From: Vriz O, et al. Age-changes in right ventricular function–pulmonary circulation coupling: from pediatric to adult stage in 1899 healthy subjects. The RIGHT Heart International NETwork (RIGHT-NET). Int J Cardiovasc Imaging 2021;37(11):3399-3411 (75).

The relationship between TAPSE and systolic pressure is nonetheless preserved across the different age bands, since the line that links the two parameters does not shift downwards when moving from the young to the old (75). In healthy subjects, therefore, the contractility of the right ventricle remains adequate to the load imposed

on it, and the fall in the ratio reflects the physiological increase in load, not a failure of contraction (75).

It follows that a reduced ratio in an older patient is not in itself a sign of dysfunction, because part of the reduction belongs to normal ageing. It is precisely for this reason that, in idiopathic pulmonary fibrosis, it is necessary to establish whether age at diagnosis is accompanied by worse coupling beyond the expected physiological change. The question is made more complex by the behaviour of the numerator, since TAPSE falls in the early stages of right ventricular remodelling and then remains relatively stable in advanced disease, so that the optimal numerator of the coupling indices might vary with age, sex and the severity of pulmonary hypertension (56).

3.7 Treatment

The first measure remains treatment of the underlying lung disease, which the guidelines recommend with a class I recommendation to optimise together with the associated conditions (25). In interstitial lung disease this includes antifibrotic agents and, when indicated, immunosuppression, alongside long-term oxygen therapy in hypoxaemic patients and pulmonary rehabilitation (25,40). Also, with a class I recommendation, patients with a suspected severe form should be referred to a specialist centre, an individualised approach should be adopted in such forms, and eligible patients should be assessed for transplantation (25).

The drugs developed for pulmonary arterial hypertension have not, on the other hand, produced results that can be transferred to this population, since the trials carried out were negative on the primary endpoint or were stopped early because a signal of harm appeared (76,77). The guidelines therefore advise against, with a class III recommendation, ambrisentan in pulmonary hypertension associated with idiopathic pulmonary fibrosis, riociguat in that associated with the idiopathic interstitial pneumonias and, more generally, the use of these drugs in the patient with lung disease and a non-severe form (25).

The only favourable result came from the INCREASE trial, in which inhaled treprostinil improved the distance walked in the walk test compared with placebo (78). On this basis the drug was approved in the United States, while the European

guidelines place it among the options that may be considered, with a class IIb recommendation (25,76). Slightly more than a quarter of the patients enrolled had idiopathic pulmonary fibrosis, however, and there is no dedicated analysis for this subgroup (78).

Lung transplantation remains the only option able to change prognosis radically in eligible patients, and the consensus document of the International Society for Heart and Lung Transplantation recommends that it be considered as early as the time of diagnosis when a usual interstitial pneumonia pattern is present (79). The listing criteria explicitly include pulmonary hypertension documented at right heart catheterisation or at echocardiography, so recognising the vascular complication directly affects when the patient is referred for transplantation (79) (Figure 19).

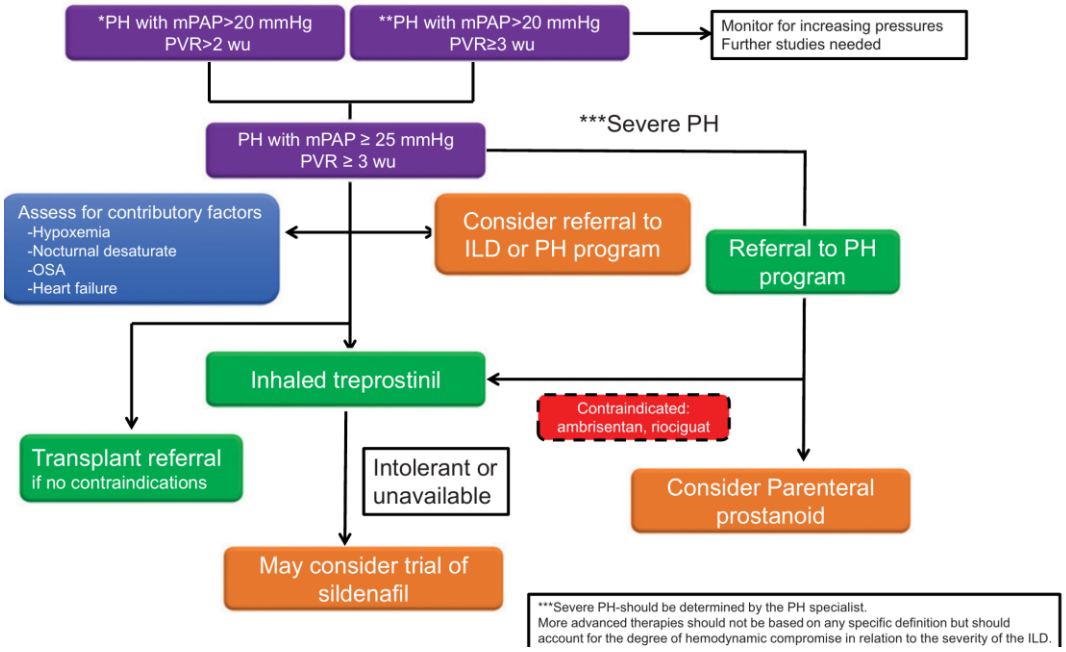


Figure 1919. Algorithm for the management of the patient with pulmonary hypertension associated with interstitial lung disease.

The asterisk indicates the definition of pulmonary hypertension of the 2022 ESC/ERS guidelines, the double asterisk that of the Sixth World Symposium. The triple asterisk indicates that the severe form should be defined by the pulmonary hypertension specialist and that the more advanced treatments should be based on the degree of haemodynamic impairment in relation to the severity of the interstitial lung disease. From: Nathan SD. Progress in the Treatment of Pulmonary Hypertension Associated with Interstitial Lung Disease. Am J Respir Crit Care Med 2023;208(3):238-246 (76).

3.8 Prognosis

In prognostic terms the weight of the complication is considerable, since in patients with advanced idiopathic pulmonary fibrosis its appearance doubles overall mortality and increases one-year mortality fivefold (37). The relationship between pressure and risk is moreover continuous: every millimetre of mercury of increase in mean pressure corresponds to a 9% rise in the risk of death (37). The association persists after adjustment both for forced vital capacity and for diffusing capacity, and the complication cannot therefore be regarded as a simple marker of advanced respiratory disease (37).

Among the five groups of the clinical classification, the forms associated with lung disease are those with the worst survival (80). Within the interstitial lung diseases the worst outcome belongs to patients with idiopathic pulmonary fibrosis, and this diagnosis is itself an independent predictor of mortality, together with forced vital capacity, diffusing capacity, systolic pulmonary artery pressure and cardiac index (81).

Echocardiographic parameters of the right heart also contribute to the prognostic estimate. Right ventricular dysfunction, dilatation of the right chambers and the ratio between ventricular diameters are independent predictors of mortality in idiopathic pulmonary fibrosis and keep their value even after adjustment for pulmonary vascular resistance (82), while the TAPSE/PAPs ratio discriminates the severe forms and predicts survival in pulmonary hypertension due to chronic lung disease (69).

4. AIM OF THE STUDY

In idiopathic pulmonary fibrosis the involvement of the right heart carries considerable prognostic weight and its recognition is often late, because the severity of respiratory impairment does not allow the severity of the vascular disease to be predicted and the guidelines do not provide for planned echocardiographic surveillance (25,37,39,40). To assess the state of the right ventricle in relation to the load it has to sustain, the TAPSE/PAPs ratio is available, a non-invasive index of ventricular-arterial coupling validated against the invasive reference measurement (70), whose clinical and prognostic meaning in fibrosing interstitial lung disease is not yet defined with the solidity documented in other conditions (69,73). Age is a prognostic determinant of the disease, it is one of the variables of the GAP index (20), and even in healthy subjects the TAPSE/PAPs ratio falls with advancing years (76).

The main aim of this study is therefore to assess whether, in patients with idiopathic pulmonary fibrosis, age at diagnosis is associated with a reduction in the TAPSE/PAPs ratio, and whether the association persists in models adjusted for sex, smoking habit and diffusing capacity of the lung for carbon monoxide. The purpose is to establish whether age at diagnosis carries its own information on the right heart, information not already contained in pulmonary function tests.

Some secondary objectives accompany this main aim. The behaviour of TAPSE and PAPs analysed separately serves to establish whether the ratio between the two parameters adds anything to each of them, while the comparison of pulmonary function between the age bands serves to understand whether patients diagnosed later come to medical attention with more advanced lung disease.

The study finally assesses the relationship between age at diagnosis and all-cause mortality, examining whether risk rises gradually with age or beyond a threshold, and compares the weight of age with that of DLCO, which among the pulmonary function tests is the parameter most indicative of pulmonary vascular involvement.

5. MATERIALS AND METHODS

5.1 Study Design and Population

The present work is an ambispective observational study, in which past data were collected retrospectively, and a proportion of the echocardiographic assessments were acquired prospectively during clinical follow-up.

The study was carried out at the Pulmonology and Cardiology outpatient clinics of the University Hospital of Modena (83). It included 198 patients with a confirmed diagnosis of idiopathic pulmonary fibrosis followed at these clinics and for whom clinical records and follow-up were available. Data collection covered the period between 2020 and 2026, while follow-up time was calculated from the date of diagnosis (83).

The diagnosis was made according to the criteria of the 2018 ATS/ERS/JRS/ALAT guidelines, at the end of a multidisciplinary discussion that combined clinical data, the findings on high-resolution computed tomography (HRCT) and, when available, histological findings (3,83). The tomographic pattern was assigned to one of the four categories provided, that is UIP, probable UIP, indeterminate for UIP and alternative diagnosis, with a note of any concomitant emphysema (3,83).

Since the study concerns the right side of the heart, cardiac and pulmonary conditions other than idiopathic pulmonary fibrosis able to alter the echocardiographic and functional parameters of interest were excluded. According to the criteria adopted for the same cohort (83), patients were therefore excluded if they presented with:

1. clinically significant left heart disease, defined by a left ventricular ejection fraction below 50%, moderate to severe diastolic dysfunction or known heart failure;
2. mitral or aortic valve disease, either stenosis or regurgitation, greater than mild;
3. congenital heart disease;
4. known pulmonary hypertension of other cause, belonging to Groups 1, 4 or 5;
5. chronic thromboembolic pulmonary disease;

6. significant obstructive ventilatory defect, defined by an FEV1/FVC ratio below 0.70 with FEV1 below 50% of predicted, or coexisting other interstitial lung disease;

7. clinical or instrumental records insufficient to assess the main study variables (83).

The population analysed includes 198 patients, with a mean age at diagnosis of 72.3 ± 8.2 years. The population was 84.3% male (167/198) and 15.7% female (31/198). Among the 192 patients with a known smoking habit, 69.8% were former smokers (134/192), 25.0% never-smokers (48/192) and 5.2% current smokers (10/192).

According to age at diagnosis, 35 patients (17.7%) were younger than 65 years, 78 (39.4%) were aged between 65 and 74 years and 85 (42.9%) were 75 years or older. At diagnosis mean FVC was 89.5 ± 19.7% of predicted and mean DLCO 55.3 ± 20.6%, while the GAP index placed 97 patients (49.2%) in stage I, 84 (42.6%) in stage II and 16 (8.1%) in stage III. Over a median follow-up of 44.6 months (IQR 23.6-73.3), 55 all-cause deaths (27.8%) were recorded (Table 2).

Table 2. General characteristics of the study population

Variable	Value	n
Demographic data		
Age at diagnosis (years), mean ± SD	72.3 ± 8.2	198
Male, n (%)	167 (84.3%)	198
Female, n (%)	31 (15.7%)	198
Smoking habit		
Never-smokers, n (%)	48 (25.0%)	192
Former smokers, n (%)	134 (69.8%)	192
Current smokers, n (%)	10 (5.2%)	192
Bands of age at diagnosis		
< 65 years, n (%)	35 (17.7%)	198
65–74 years, n (%)	78 (39.4%)	198
≥ 75 years, n (%)	85 (42.9%)	198
Pulmonary function tests		
FVC, % predicted, mean ± SD	89.5 ± 19.7	197
DLCO, % predicted, mean ± SD	55.3 ± 20.6	188
Echocardiographic parameters		
TAPSE (mm), mean ± SD	20.57 ± 4.19	81
PAPs (mmHg), mean ± SD	39.19 ± 16.71	112
TAPSE/PAPs (mm/mmHg), mean ± SD	0.62 ± 0.35	71
GAP index		
GAP, mean ± SD	3.60 ± 1.29	197
GAP, median (IQR)	4.0 (3.0–5.0)	197
Stage I, n (%)	97 (49.2%)	197

Stage II, n (%)	84 (42.6%)	197
Stage III, n (%)	16 (8.1%)	197
Outcome		
Follow-up (months), median (IQR)	44.6 (23.6–73.3)	197
Deaths, n (%)	55 (27.8%)	198

SD: standard deviation; IQR: interquartile range; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; TAPSE: tricuspid annular plane systolic excursion; PAPs: systolic pulmonary artery pressure. The n column indicates the number of patients with the value available. Pulmonary function parameters refer to the assessment performed at the time of diagnosis, whereas echocardiographic parameters come from the assessment performed during clinical follow-up.

5.2 Pulmonary Function Tests

Pulmonary function data were obtained from the reports of the tests performed at the time of diagnosis, as part of routine clinical assessment at the Pulmonology service, in accordance with ATS/ERS technical standards (83–86).

The parameters considered were forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), total lung capacity (TLC), single-breath diffusing capacity of the lung for carbon monoxide (DLCO) and the same parameter corrected for alveolar volume (DLCO/VA) (83). All values were expressed as a percentage of predicted according to the reference equations in use at the pulmonary function laboratory.

DLCO was taken as the main measure of gas exchange (83) and, in the dedicated analyses, as the term of comparison with age at diagnosis. For each patient the GAP index was finally calculated, which combines sex, age, FVC and DLCO into a score from which assignment to one of the three risk stages follows (20).

5.3 Echocardiographic Assessment

Transthoracic echocardiographic examinations were performed during clinical follow-up by experienced cardiologists, according to the recommendations of the American Society of Echocardiography and of the European Association of Cardiovascular Imaging (52,56,83). The examination included the routine assessment of the left side of the heart, but data collection focused on the right side and on the pulmonary circulation (83).

TAPSE (mm) was measured in M-mode in the apical four-chamber view, with the cursor aligned on the lateral tricuspid annulus, as the total displacement of the annular

plane between end-diastole and end-systole (50). Systolic pulmonary artery pressure (PAPs, mmHg) was estimated from the peak velocity of tricuspid regurgitation using the simplified Bernoulli equation, adding to the gradient the right atrial pressure derived from the diameter and inspiratory collapsibility of the inferior vena cava (83).

The ratio between the two measurements gave the TAPSE/PAPs ratio (mm/mmHg), used as a non-invasive index of coupling between the right ventricle and the pulmonary circulation (70). In patients in whom TAPSE or PAPs could not be quantified reliably, because of the absence of an adequate tricuspid regurgitation profile, a suboptimal acoustic window or the lack of a record in the report, the value was considered missing for the corresponding analyses (83).

5.4 Database Construction and Data Collection

A dedicated electronic database was built for the present work, fed from several hospital information systems. Its construction required the systematic retrieval of clinical, functional, laboratory and echocardiographic data, with a check of the completeness and consistency of each variable.

Pulmonological and radiological information was entered by the specialists of the Centre for Rare Lung Diseases. It includes the date of diagnosis, the tomographic pattern with any concomitant emphysema, pulmonary function tests and antifibrotic treatment, for which the drug used, the dates of start and discontinuation, the reasons for stopping and any subsequent lines were recorded.

The comorbidity and cardiovascular risk profile was reconstructed from the reports of the specialist outpatient clinic. From these were obtained the smoking habit, divided into never-smoker, former smoker and current smoker, and the presence of arterial hypertension, dyslipidaemia, diabetes mellitus and chronic kidney disease, together with height and weight for the calculation of body mass index (83). Body surface area was instead taken from the echocardiographic report.

Laboratory parameters were obtained through the hospital information system (Data Warehouse). For haemoglobin, MCV, MCHC and RDW the most recent value was selected, whereas for uric acid, 25-hydroxy-vitamin D and parathyroid hormone, which are measured less often, the search was extended backwards to 2020. When

vitamin D and parathyroid hormone were not present in the Data Warehouse, the Electronic Health Record was consulted.

A mixed methodology was adopted for the echocardiographic data. Past assessments were reconstructed retrospectively by selecting the most recent examination performed between 2020 and 2026, through a cross-search between the Data Warehouse, the Electronic Health Record and the InfoClin platform, while for the patients assessed prospectively at the dedicated outpatient clinic, as part of clinical follow-up, the parameters were acquired directly through InfoClin.

The mainly retrospective nature of the collection resulted in different availability of the individual parameters and every analysis was therefore carried out only on the cases with the value available (83).

Finally, vital status and the date of death, where applicable, were obtained from the clinical records and from the hospital Data Warehouse, and follow-up time was calculated from the date of diagnosis to the date of death or, in living patients, to that of the last documented contact.

5.5 Ethical Aspects

The project was conducted as a single-centre clinical audit within a thesis with a mainly educational purpose, in accordance with the institutional guidelines of the University of Modena and Reggio Emilia applicable to this type of academic activity.

Only pseudonymised data generated during normal clinical practice were analysed. The project did not involve the assignment of diagnostic or therapeutic strategies, the performance of additional tests or procedures, direct contact with participants or any change in clinical management, and all care decisions were taken independently by the physicians responsible for treatment.

Vital status was determined only through clinical records and health administrative sources already available, without contacting participants. Data were handled in accordance with the applicable institutional procedures and with Regulation (EU) 2016/679 on the protection of personal data, and no information allowing direct identification of participants is reported.

Because of these characteristics, and in accordance with the institutional procedures applicable to clinical audits conducted within thesis projects, neither assessment and approval by an Ethics Committee nor the acquisition of specific informed consent was required.

5.6 Statistical Analysis

The analysis was designed to assess the relationship between age at diagnosis and pulmonary function, the echocardiographic parameters of the right heart, ventricular-arterial coupling and all-cause mortality. Continuous variables were expressed as mean ± standard deviation or as median and interquartile range (IQR), and categorical variables as absolute frequencies and percentages.

The cohort was first divided into three bands of age at diagnosis, below 65 years, between 65 and 74 years and 75 years or older. The comparison of respiratory and echocardiographic parameters between the three bands was carried out with the non-parametric Kruskal-Wallis test. The relationship between age, treated as a continuous variable, and the other continuous variables was instead described with the Spearman rank correlation coefficient.

The relationship between age and echocardiographic parameters was then studied with linear regression models, estimated first with age alone and then adding sex and smoking habit. TAPSE, PAPs and the TAPSE/PAPs ratio were all analysed as continuous variables. The comparison between the two models made it possible to check whether any association with age remained once these two factors were considered, and for each model the β coefficient, expressed per year of age, and its 95% confidence interval were reported.

For mortality, age was compared between deceased and surviving patients with the Mann-Whitney U test, while the distribution of deaths across the three bands was assessed with the chi-square test. The same Mann-Whitney test, and the chi-square test for sex, were also used to compare the main functional and echocardiographic characteristics between the two groups.

Age was then entered into logistic regression models, both as a continuous variable, estimating the odds ratio per year, and dichotomised at 65 years, the threshold above

which the GAP index assigns the maximum score for age (20). The models were estimated without adjustment, then adjusted for sex and smoking habit and, for continuous age, also for DLCO and FVC.

Finally, to separate the contribution of age from that of gas exchange, models including age and DLCO simultaneously were built. The echocardiographic parameters, which are continuous variables, were analysed with linear regression, and mortality, which is a dichotomous variable, with logistic regression.

A p value below 0.05 was considered statistically significant and the analyses were carried out with IBM SPSS Statistics software, version 26 (IBM Corp., Armonk, NY, USA) (83).

6. RESULTS

6.1 Age at Diagnosis and Pulmonary Function

The main pulmonary function parameters were compared between the three bands of age at diagnosis and showed no statistically significant differences (Table 3). DLCO went from 61.35 ± 21.62% of predicted in patients younger than 65 years to 53.43 ± 19.15% above 75 years, with a downward trend that did not reach significance (p = 0.167).

Table 3. Pulmonary function tests in the three bands of age at diagnosis

Variable	< 65 years (n = 35)	65–74 years (n = 78)	≥ 75 years (n = 85)	p
DLCO, % predicted	61.35 ± 21.62	54.59 ± 21.45	53.43 ± 19.15	0.167
FVC, % predicted	88.80 ± 20.10	88.59 ± 19.35	90.61 ± 20.14	0.936
FEV1, % predicted	90.54 ± 19.49	94.60 ± 18.84	98.87 ± 19.42	0.159
TLC, % predicted	85.63 ± 17.99	85.62 ± 15.78	84.54 ± 16.48	0.892
DLCO/VA, % predicted	72.53 ± 15.47	70.97 ± 20.90	67.02 ± 23.30	0.360

Values expressed as mean ± standard deviation; comparison by Kruskal-Wallis test. The number of patients indicated for each band refers to the band as a whole, and the actual number may be lower for individual parameters. FEV1: forced expiratory volume in the first second; TLC: total lung capacity; DLCO/VA: DLCO corrected for alveolar volume.

Even treating age at diagnosis as a continuous variable, no correlation with the respiratory parameters reached statistical significance (Table 4). The highest coefficient in absolute value was that of DLCO (ρ = -0.126; p = 0.086).

Table 4. Spearman correlations between age at diagnosis and functional and echocardiographic parameters

Variable	Spearman ρ	p	n
Pulmonary function tests			
DLCO, % predicted	−0.126	0.086	188
FVC, % predicted	−0.002	0.983	197
FEV1, % predicted	+0.124	0.083	197
TLC, % predicted	−0.042	0.558	194
DLCO/VA, % predicted	−0.075	0.300	191
Echocardiographic parameters			
TAPSE (mm)	−0.146	0.193	81
PAPs (mmHg)	+0.136	0.152	112
TAPSE/PAPs (mm/mmHg)	−0.220	0.066	71

ρ: Spearman rank correlation coefficient, calculated with respect to age at diagnosis treated as a continuous variable. FVC: forced vital capacity (% predicted); FEV1: forced expiratory volume in the first second (% predicted); TLC: total lung capacity (% predicted); DLCO: diffusing capacity of the lung for carbon monoxide (% predicted); DLCO/VA: diffusing capacity corrected for alveolar volume (% predicted); TAPSE: tricuspid annular plane systolic excursion (mm); PAPs: estimated systolic pulmonary artery pressure (mmHg); TAPSE/PAPs: ratio between the two parameters (mm/mmHg).

6.2 Age at Diagnosis and Echocardiographic Parameters of the Right Heart

In the unadjusted comparison between the three age bands there were no statistically significant differences for TAPSE (p = 0.468), for PAPs (p = 0.476) or for the TAPSE/PAPs ratio, which was 0.76 ± 0.52 mm/mmHg in patients younger than 65 years, 0.58 ± 0.30 between 65 and 74 years and 0.57 ± 0.21 above 75 years (p = 0.319) (Table 5).

Table 5. Echocardiographic parameters in the three bands of age at diagnosis

Variable	< 65 years (n = 18–25)	65–74 years (n = 26–44)	≥ 75 years (n = 27–43)	p
TAPSE (mm)	21.39 ± 4.22	20.19 ± 4.86	20.48 ± 3.41	0.468
PAPs (mmHg)	36.68 ± 15.24	41.11 ± 20.20	38.67 ± 13.41	0.476
TAPSE/PAPs (mm/mmHg)	0.76 ± 0.52	0.58 ± 0.30	0.57 ± 0.21	0.319

Values expressed as mean ± standard deviation; comparison by Kruskal-Wallis test. The ranges of numbers reflect the different availability of the individual parameters. TAPSE: tricuspid annular plane systolic excursion (mm); PAPs: estimated systolic pulmonary artery pressure (mmHg); TAPSE/PAPs: ratio between the two parameters (mm/mmHg).

In the Spearman correlations with continuous age no echocardiographic parameter reached statistical significance; the highest coefficient in absolute value was that of the TAPSE/PAPs ratio (ρ = -0.220; p = 0.066) (Table 4).

In the linear regression models, age at diagnosis was significantly associated with the TAPSE/PAPs ratio, both in the unadjusted model (β = -0.011 per year; p = 0.019) and in the model adjusted for sex and smoking habit (β = -0.010 per year; p = 0.034). The association with age was not significant either for TAPSE or for PAPs considered separately (Table 6).

Table 6. Linear regression between age at diagnosis and echocardiographic parameters

Outcome	Model	β (per year)	95% CI	p	n
TAPSE (mm)	Unadjusted	−0.064	−0.171; +0.044	0.244	81
	Adjusted for sex and smoking	−0.032	−0.145; +0.080	0.569	80
PAPs (mmHg)	Unadjusted	+0.264	−0.124; +0.652	0.182	112
	Adjusted for sex and smoking	+0.307	−0.092; +0.707	0.130	111
TAPSE/PAPs (mm/mmHg)	Unadjusted	−0.011	−0.020; −0.002	**0.019**	71
	Adjusted for sex and smoking	−0.010	−0.020; −0.001	**0.034**	70

β: change in the outcome for every year of increase in age at diagnosis; 95% CI: 95% confidence interval; n: number of patients included in the model. The adjusted model includes sex and smoking habit. TAPSE: tricuspid annular plane systolic excursion (mm); PAPs: estimated systolic pulmonary artery pressure (mmHg); TAPSE/PAPs: ratio between the two parameters (mm/mmHg). Statistically significant values are shown in bold.

The distribution of the individual values as a function of age and the comparison between the three bands are shown in Figures 20 and 21.

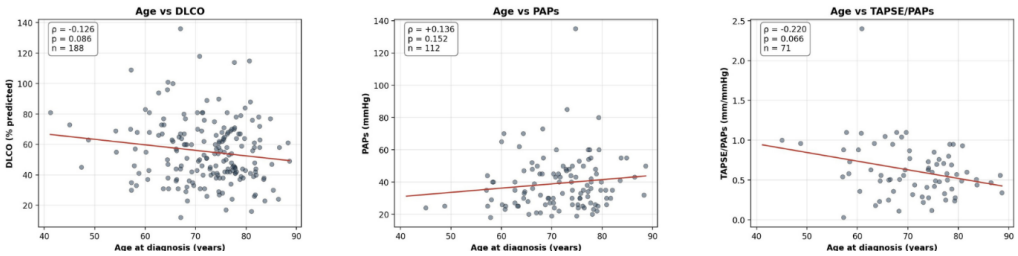


Figure 20. Relationship between age at diagnosis and DLCO, estimated systolic pulmonary artery pressure and the TAPSE/PAPs ratio.

Each point represents one patient and the line indicates the linear trend; each panel reports the Spearman correlation coefficient, the p value and the number of patients. DLCO: diffusing capacity of the lung for carbon monoxide; PAPs: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion.

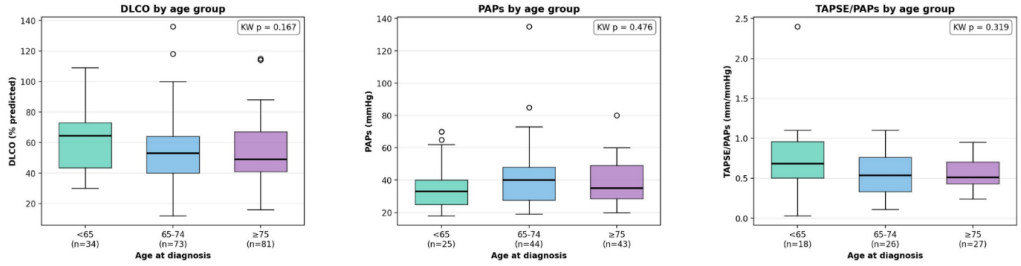


Figure 21. Distribution of DLCO, estimated systolic pulmonary artery pressure and the TAPSE/PAPs ratio in the three bands of age at diagnosis.
The central line indicates the median, the box the interquartile range, the whiskers the extreme values that are not outliers and the circles the outliers. KW: p value at the Kruskal-Wallis test.

The effect of age at diagnosis on the three echocardiographic parameters in the models adjusted for sex and smoking habit is shown in Figure 22, with each coefficient expressed as a percentage change per ten years relative to the mean value of the cohort.

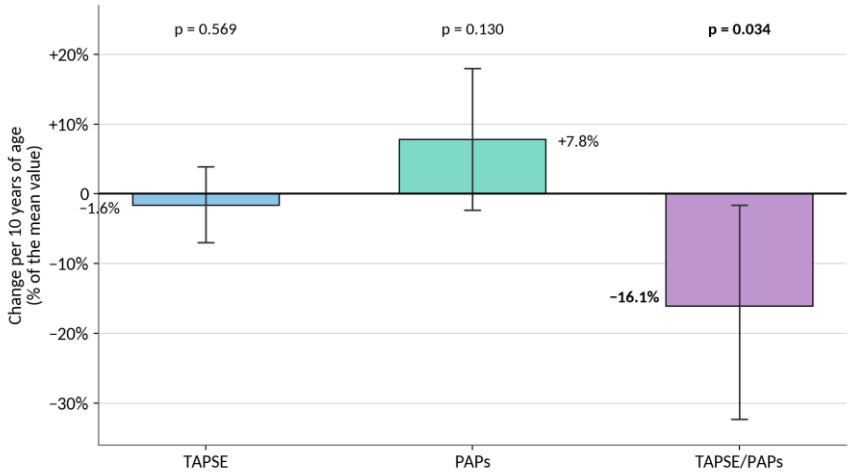


Figure 22. Estimated change in TAPSE, PAPs and the TAPSE/PAPs ratio per ten years of age at diagnosis, in the linear regression models adjusted for sex and smoking habit.
The height of the bars indicates the estimate and the vertical lines the 95% confidence interval, expressed as a percentage of the mean value of each parameter in the cohort. The value of the estimate is reported next to the bars and the p value above, in bold when the association is statistically significant. TAPSE: tricuspid annular plane systolic excursion; PAPs: systolic pulmonary artery pressure.

6.3 Age at Diagnosis and Mortality

Mean age at diagnosis was 74.09 ± 6.02 years in the 55 patients who died and 71.59 ± 8.85 years in the 143 survivors, with no statistically significant difference (p = 0.203) (Table 8). The distribution of deaths across the three age bands was instead significantly different (p = 0.003), with a mortality of 5.7% (2/35) in patients younger than 65 years, 37.2% (29/78) between 65 and 74 years and 28.2% (24/85) above 75 years (Table 7, section A).

In the logistic regression models, age considered as a continuous variable did not reach statistical significance in any of the three models, remaining consistently at the margin (p values between 0.051 and 0.058). Age of 65 years or older was instead significantly associated with mortality, with an odds ratio of 7.95 in the unadjusted model and of 8.00 in the model adjusted for sex and smoking habit (p = 0.006 in both) (Table 7, section B).

Table 7. Age at diagnosis and all-cause mortality

A. Mortality in the three bands of age at diagnosis

Age band	Deceased	Survivors	p
< 65 years (n = 35)	2 (5.7%)	33 (94.3%)	**0.003**
65–74 years (n = 78)	29 (37.2%)	49 (62.8%)	
≥ 75 years (n = 85)	24 (28.2%)	61 (71.8%)	

B. Logistic regression models

Predictor	Model	OR	95% CI	p	n
Age (per year)	Unadjusted	1.041	0.999–1.085	0.058	198
	Adjusted for sex and smoking	1.045	1.000–1.092	0.051	192
	Adjusted for sex, smoking, DLCO and FVC	1.046	0.999–1.096	0.057	182
Age ≥ 65 vs < 65 years	Unadjusted	7.95	1.84–34.39	**0.006**	198
	Adjusted for sex and smoking	8.00	1.83–34.98	**0.006**	192

Section A: chi-square test on the three bands. Section B: logistic regression with all-cause mortality as the dependent variable. OR: odds ratio; 95% CI: 95% confidence interval; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity. Statistically significant values are shown in bold.

The distribution of mortality across the three age bands is shown in Figure 23.

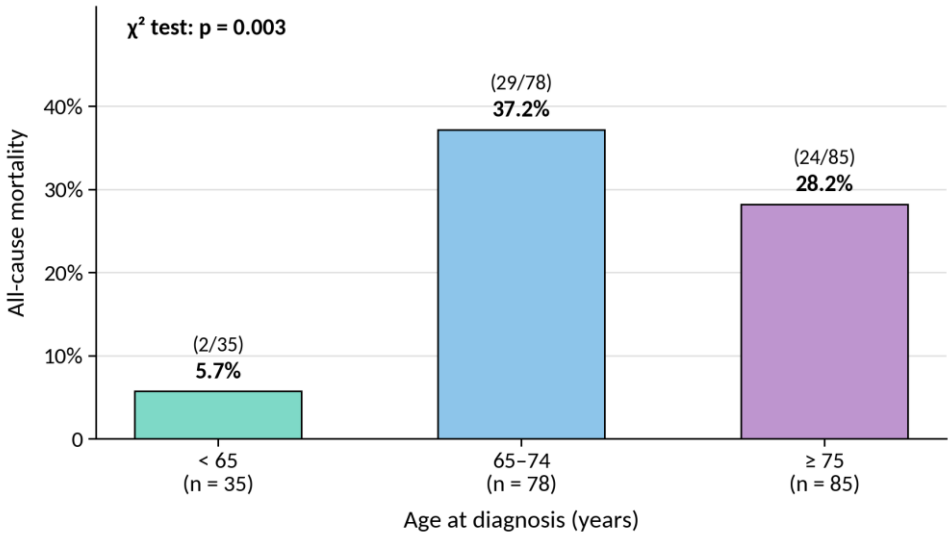


Figure 23. All-cause mortality in the three bands of age at diagnosis.
Above each bar are reported the percentage of deaths and the number of deceased patients out of the total for that band; the p value at the chi-square test is reported at the top. The colours of the three bands correspond to those used in Figure 23. n: number of patients.

In the comparison between survivors and deceased patients the distribution by sex was not significantly different ($p = 0.357$). Patients who died had lower values of FVC (81.78 ± 18.23% versus 92.47 ± 19.56%; $p = 0.001$) and of DLCO (48.63 ± 18.66% versus 58.01 ± 20.81%; $p = 0.007$) and a higher GAP index (4.11 ± 1.27 versus 3.40 ± 1.25; $p < 0.001$).

On the echocardiographic side, patients who died had a lower TAPSE (18.57 ± 4.99 versus 21.36 ± 3.57 mm; $p = 0.003$), a higher PAPs (48.81 ± 22.44 versus 35.34 ± 11.93 mmHg; $p < 0.001$) and a lower TAPSE/PAPs ratio (0.41 ± 0.25 versus 0.70 ± 0.35 mm/mmHg; $p < 0.001$) (Table 8).

Table 8. Characteristics of surviving and deceased patients

Variable	Survivors (n = 143)	Deceased (n = 55)	p
Age at diagnosis (years), mean ± SD	71.59 ± 8.85	74.09 ± 6.02	0.203
Male, n (%)	118 (82.5%)	49 (89.1%)	0.357
Female, n (%)	25 (17.5%)	6 (10.9%)	
FVC, % predicted, mean ± SD	92.47 ± 19.56	81.78 ± 18.23	**0.001**
DLCO, % predicted, mean ± SD	58.01 ± 20.81	48.63 ± 18.66	**0.007**
GAP index, mean ± SD	3.40 ± 1.25	4.11 ± 1.27	**< 0.001**
TAPSE (mm), mean ± SD	21.36 ± 3.57 (n = 58)	18.57 ± 4.99 (n = 23)	**0.003**
PAPs (mmHg), mean ± SD	35.34 ± 11.93 (n = 80)	48.81 ± 22.44 (n = 32)	**< 0.001**
TAPSE/PAPs (mm/mmHg), mean ± SD	0.70 ± 0.35 (n = 51)	0.41 ± 0.25 (n = 20)	**< 0.001**

Values expressed as mean ± standard deviation; comparison by Mann-Whitney U test for continuous variables and chi-square test for sex. For the echocardiographic parameters the number available in each group is given in brackets. FVC: forced vital capacity (% predicted); DLCO: diffusing capacity of the lung for carbon monoxide (% predicted); GAP: Gender-Age-Physiology index (score); TAPSE: tricuspid annular plane systolic excursion (mm); PAPs: estimated systolic pulmonary artery pressure (mmHg); TAPSE/PAPs: ratio between the two parameters (mm/mmHg). Statistically significant values are shown in bold.

The TAPSE/PAPs ratio in surviving and deceased patients is shown in Figure 24.

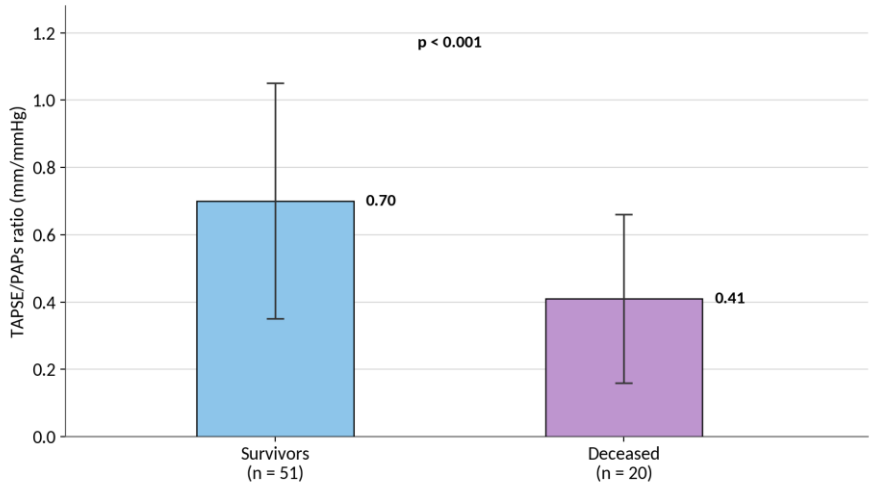


Figure 24. TAPSE/PAPs ratio in surviving (light blue) and deceased (lilac) patients.
The bars indicate the mean and the vertical lines the standard deviation; the mean value is reported next to each bar and the p value at the Mann-Whitney U test at the top. TAPSE: tricuspid annular plane systolic excursion; PAPs: systolic pulmonary artery pressure; n: number of patients with the value available.

6.4 Joint Contribution of Age at Diagnosis and DLCO

In the models including age at diagnosis and DLCO simultaneously (Table 9), only DLCO was significant for PAPs (β = -0.248 per percentage point; p = 0.002), while age did not reach significance.

For the TAPSE/PAPs ratio both age (β = -0.011 per year; p = 0.019) and DLCO (β = +0.006 per percentage point; p = 0.013) were significant, with a proportion of variability explained by the model of 17.1%. For TAPSE neither of the two predictors reached significance.

In the logistic regression model for mortality, DLCO was significantly associated (OR 0.98 per percentage point; p = 0.011), while age did not reach significance (p = 0.085).

Table 9. Joint contribution of age at diagnosis and DLCO to the parameters of the right heart and to mortality

Outcome	Predictor	Coefficient	95% CI	p	Model
TAPSE (mm)	Age (per year)	−0.054	−0.164; +0.057	0.342	n = 77; R^2 = 0.053
	DLCO (per % predicted)	+0.041	−0.006; +0.088	0.088	
PAPs (mmHg)	Age (per year)	+0.245	−0.132; +0.622	0.207	n = 107; R^2 = 0.107
	DLCO (per % predicted)	−0.248	−0.402; −0.094	**0.002**	
TAPSE/PAPs (mm/mmHg)	Age (per year)	−0.011	−0.020; −0.002	**0.019**	n = 67; R^2 = 0.171
	DLCO (per % predicted)	+0.006	+0.001; +0.010	**0.013**	
Mortality (OR)	Age (per year)	1.04	0.99–1.08	0.085	n = 188
	DLCO (per % predicted)	0.98	0.96–0.99	**0.011**	

For the echocardiographic parameters the coefficients come from multivariable linear regression models, and for mortality from a logistic regression model in which the coefficient is expressed as an odds ratio (OR). R^2: proportion of the variability of the outcome explained by the model; 95% CI: 95% confidence interval. Statistically significant values are shown in bold.

7. DISCUSSION

7.1 Summary of the Main Findings

The present work focuses on the relationship between age at diagnosis and coupling between the right ventricle and the pulmonary circulation in patients with idiopathic pulmonary fibrosis and examines its consequences for pulmonary function and for mortality.

There are four main findings. In the cohort, age at diagnosis was not associated with greater respiratory impairment, and patients diagnosed later therefore did not have, at the time of diagnosis, worse lung function. Older age corresponds instead to a lower TAPSE/PAPs ratio, also in the models adjusted for sex, smoking habit and diffusing capacity, while the same association does not appear for TAPSE and PAPs considered separately.

The risk of death, moreover, does not rise gradually with age but is clearly higher in patients diagnosed at 65 years or older, and those who died were not distinguished by chronological age but by the state of the right heart. Diffusing capacity, finally, remained the strongest predictor of pulmonary pressure and of mortality, while age was independently associated only with the coupling index.

This is therefore not a generic right ventricular dysfunction of the older patient, but a reduction in coupling associated with age and not explained by respiratory impairment alone.

7.2 Age at Diagnosis and Pulmonary Function

In the cohort examined, no pulmonary function parameter differed between the three age bands, and the correlations with age treated as a continuous variable did not reach significance either (Tables 3 and 4). The finding should be described as the absence of a demonstrable cross-sectional association, and not as proof that age does not influence lung function, since for DLCO the values still tend to be lower in patients diagnosed at an older age.

The distinction is not merely formal. A cross-sectional study describes the disease at a single moment and does not follow its evolution, so the absence of differences

between the age bands indicates that at diagnosis older patients do not have greater respiratory impairment, but it does not allow us to exclude that age affects the subsequent course.

This finding is nonetheless useful for interpreting the ones that follow. The association between age and coupling described in the next section cannot be attributed to more advanced lung disease in older patients, because it persists in the model that includes diffusing capacity (Table 9), that is at equal values of the functional parameter most closely linked to vascular involvement.

7.3 Age at Diagnosis and Ventricular-Arterial Coupling

The central finding of this work concerns the TAPSE/PAPs ratio, which was the only echocardiographic parameter associated with age at diagnosis. The association was maintained both in the model adjusted for sex and smoking habit and in the one including DLCO, and corresponds, in clinical terms, to a reduction of the ratio of about 0.10 mm/mmHg for every ten years of age at diagnosis.

The estimated value remained substantially unchanged when moving from the model with age alone to those including sex, smoking habit and diffusing capacity (Tables 6 and 9). The estimate therefore does not depend on the distribution of these factors between younger and older patients.

It should be noted that the association does not emerge from simple correlation. Treating age as a continuous variable, the Spearman coefficient of the TAPSE/PAPs ratio was the highest among those of the echocardiographic parameters but did not reach significance, which appeared instead in the linear regression models, both in the one with age alone and in the adjusted ones. The difference depends on the method, since Spearman correlation uses only the ranking of the patients, whereas linear regression estimates the size of the change per year of age. The effect is therefore small: it becomes visible when its size is measured year by year, but it is not large enough to separate younger from older patients clearly.

The fact that age is associated neither with TAPSE nor with PAPs considered separately supports the interpretation of the ratio as a more sensitive indicator of early uncoupling. TAPSE describes the longitudinal function of the right ventricle and PAPs

the load against which it works, so two patients with the same pulmonary pressure may have a very different ventricular adaptation (45), which only the ratio between the two measurements allows to be recognised.

It follows that a slight reduction in TAPSE and a slight increase in PAPs, which are not significant when assessed separately, translate into a significant reduction of the ratio. This behaviour is consistent with what is known about the right ventricle exposed to a chronic load, in which the ratio between contractility and load falls already in the early stages, while clear uncoupling becomes apparent at rest only later (45).

The literature offers several confirmations of this sequence. In chronic lung disease the rise in vascular resistance is slow and the right ventricle remains compensated for a long time, with the systolic parameters in common use within the normal range (40), and the echocardiographic recommendations point out that a normal TAPSE does not exclude dysfunction of the right chamber (56).

The same is seen in idiopathic pulmonary fibrosis. In the early stages TAPSE is similar to that of healthy controls while wall deformation is already reduced (58), and in a series of fibrosing interstitial lung diseases compared with age-matched controls TAPSE does not differ between the two groups, whereas the TAPSE/PAPs ratio is significantly lower (73).

Compared with these observations, the present work adds two elements. The first is that the reduction in coupling is associated with age at diagnosis and not only with the severity of functional impairment. The direction was already suggested by the literature, since in pulmonary hypertension associated with chronic lung disease the TAPSE/PAPs ratio does not correlate with total lung capacity or with vital capacity (69).

The second element concerns diffusing capacity. Age keeps an association of its own with the ratio even when DLCO is included in the model (Table 9), so the information that age carries about the right heart is not already contained in the functional parameter most closely linked to vascular involvement.

The contribution of physiological ageing remains to be considered. In healthy subjects the TAPSE/PAPs ratio falls with age without contractility becoming inadequate to the load, since the relationship between TAPSE and systolic pressure is

preserved across the different age bands (75). Part of the reduction observed therefore belongs to the normal ageing of the pulmonary circulation.

The present study has no healthy control group and therefore does not allow the physiological share to be separated from the pathological one. The estimated reduction, of about 0.10 mm/mmHg per decade, is moreover close to the one described in healthy subjects (75), and the data available do not allow us to state that in idiopathic pulmonary fibrosis coupling falls with age more rapidly than it does physiologically.

What the data do show concerns the level of the ratio rather than the speed at which it falls. The mean value of patients aged 75 years or older, 0.57 mm/mmHg, is clearly lower than the one described in healthy subjects of the same age (75), and the mean value of the cohort, 0.62 mm/mmHg, is similar to the one reported in fibrosing interstitial lung diseases compared with controls of the same age, where the ratio is lower than in those controls (73). Whatever the mechanism, age at diagnosis identifies patients with worse coupling among patients that pulmonary function tests do not distinguish.

7.4 Age at Diagnosis, Coupling and Mortality

The relationship between age and survival was not linear. Considered as a continuous variable, age was associated with mortality only at the margin of significance, whereas patients diagnosed at 65 years or older showed a clearly higher probability of death, with an odds ratio of 8.00 (95% CI 1.83-34.98) compared with those diagnosed before that age.

This pattern corresponds to the structure of the GAP index, which assigns the maximum score for age precisely above 65 years (20) and is the reason why that threshold was adopted a priori in this analysis. The result is therefore consistent with the weight that the index gives to age, and the threshold keeps its meaning even when sex and smoking habit are included in the model.

Some elements nonetheless limit the scope of this finding. The highest mortality was observed in the band between 65 and 74 years and not in the oldest one, and below 65 years only two deaths occurred (Table 7). The size of the increase in risk above 65 years therefore requires series with a larger number of events.

The comparison between survivors and deceased patients adds an important element. The two groups did not differ either in age at diagnosis or in sex, whereas the patients who died had a clearly worse cardiopulmonary profile, with less favourable values of FVC, DLCO and GAP index and with all three echocardiographic parameters altered in the expected direction. Those who died were therefore distinguished not by chronological age but by the state of the right heart and by the severity of functional impairment.

The most significant finding concerns the TAPSE/PAPs ratio, which averaged 0.41 mm/mmHg in the deceased against 0.70 mm/mmHg in the survivors. Both values are lower than those described in healthy subjects of corresponding age (75), but the value of the deceased lies at the upper limit of the range that the echocardiographic recommendations associate with uncoupling and with an increased risk of death (56), and below the threshold of 0.55 mm/mmHg that the guidelines include among the signs suggestive of pulmonary hypertension (25).

The finding is relevant because in the series of fibrosing interstitial lung diseases mentioned earlier the TAPSE/PAPs ratio had not reached prognostic significance (73), whereas in the present cohort it distinguishes the deceased from the survivors with the highest level of significance among the echocardiographic parameters considered.

The comparison between survivors and deceased patients was made with the Mann-Whitney U test and therefore describes the values observed in the two groups, without taking the time elapsed until the event into account. What it shows is that the patients who died already had clearly worse coupling at the time of the echocardiographic assessment.

7.5 The Role of DLCO

DLCO was confirmed as the factor most firmly associated with pulmonary vascular involvement and with prognosis, while age was independently associated only with the coupling index. The two variables therefore carry partly distinct information, and the assessment of the right heart cannot be reduced to pulmonary function alone.

The finding is expected and consistent with the literature. DLCO reflects the integrity of the alveolar-capillary interface and of the microvascular bed, is lower in

patients with established pulmonary hypertension (36) and, in the same population as the present study, lower values are associated with higher pulmonary pressure and with worse coupling (83).

Age and DLCO nonetheless provide partly different information. DLCO reflects above all the extent of pulmonary vascular involvement and the risk of death, whereas age at diagnosis is associated with the ability of the right ventricle to adapt to load, and it keeps this association even when DLCO is included in the model.

In the models including both variables, moreover, neither of the two was associated with TAPSE considered alone, whereas both were associated with the ratio (Table 9). The information therefore lies in the relationship between function and load and not in the measure of function alone.

It follows that diffusing capacity alone is not enough to identify the patients in whom the state of the right heart deserves a dedicated assessment. Age and DLCO together account for 17.1% of the variability of the TAPSE/PAPs ratio (Table 9), so other factors not considered in this analysis contribute to it.

7.6 Clinical Implications

In the patient with lung disease the guidelines recommend echocardiography when pulmonary hypertension is already suspected, and they do not provide for periodic checks in subjects at risk (25). Clinical suspicion is, however, difficult to form, because exertional dyspnoea, the dominant symptom of pulmonary hypertension, overlaps with that of the underlying lung disease (25), and the severity of the lung disease does not predict that of the vascular disease (39).

The consequence, in clinical practice, is late recognition of the complication, documented by the small proportion of patients with interstitial lung disease who reach right heart catheterisation and by the proportion of these who already have a severe form at the time of the examination (39).

In this context the TAPSE/PAPs ratio has a practical advantage, because it is obtained from two measurements that are already among the parameters the recommendations indicate should be acquired and reported in the assessment of the right side of the heart (50), without invasive procedures or dedicated software (53,69).

It can therefore be calculated in every patient with idiopathic pulmonary fibrosis who undergoes the examination during follow-up.

The results of this study identify an element that could guide the choice of the patients to be reassessed. Age at diagnosis is available for every patient without any need for investigations, it is independently associated with a lower TAPSE/PAPs ratio even at equal diffusing capacity, and patients diagnosed at 65 years or older showed a clearly higher mortality in the cohort (OR 8.00; 95% CI 1.83-34.98).

Since echocardiography is requested only when the clinical findings are not explained by respiratory impairment (25), age at diagnosis could be used to identify the patients in whom the examination should be repeated during follow-up, calculating the TAPSE/PAPs ratio on that occasion.

The study cannot test this idea, because it did not look at whether repeating the examination in this way changes clinical management or survival. It should also be remembered that in pulmonary hypertension associated with interstitial lung disease the treatment options remain limited (76,77).

What the data support is that age at diagnosis and the TAPSE/PAPs ratio carry information about the right heart that pulmonary function tests do not provide, and that this information is obtained without dedicated investigations.

7.7 Strengths and Limitations of the Study

Among the strengths of this work are the size of the cohort, which is considerable for a rare disease followed in a single centre, the consistency of the diagnostic criteria, applied with multidisciplinary discussion, and the fact that the data come from real clinical practice, that is from the setting in which the TAPSE/PAPs ratio would actually be used (83).

The internal consistency of the results adds to this. The association between age and coupling was maintained in all the models, from the unadjusted one to the one including DLCO, and the same direction emerges from the comparison between survivors and deceased patients, in which the TAPSE/PAPs ratio separates the two groups with the highest level of significance, together with estimated pulmonary pressure and the GAP index.

The work also has limitations inherent in its observational design. The TAPSE/PAPs ratio could be calculated in slightly more than a third of the patients, mainly because of the absence of a measurable tricuspid regurgitation, a well-known difficulty in advanced lung disease (60). Since the calculation requires an adequate regurgitation profile, a finding that is more easily obtained when the right chambers are already involved, the patients with the value available may not represent the whole cohort, as also noted in the study conducted on the same population (83).

Pulmonary pressure was moreover estimated with echocardiography and not measured with right heart catheterisation, which remains the diagnostic reference. The parameters analysed should therefore be understood as echocardiographic indices and not as haemodynamic measurements, with the qualification that it is precisely their availability in everyday practice that makes them of interest as a surveillance tool.

The single-centre and mainly retrospective design requires confirmation in independent series (83), and the interval between diagnosis and echocardiography is not uniform across patients. These limitations concern above all the precision of the estimates and their generalisability, whereas the direction of the main results remained constant across the different analyses carried out in this study.

7.8 Future Perspectives

The results open several lines of work. The first is confirmation of the association between age at diagnosis and coupling in multicentre series and with a common echocardiographic protocol, to reduce both the proportion of missing data and the variability linked to the moment at which the examination is performed.

The second concerns reference values. The echocardiographic recommendations point out that the ratio changes with age even in healthy subjects and that its numerator might behave differently depending on age and sex (56), so that age-specific thresholds would make it possible to distinguish the physiological from the pathological reduction in the individual patient.

A third line is longitudinal assessment. Serial changes in echocardiographic parameters improve predictive ability compared with a single measurement (56), so following the TAPSE/PAPs ratio over time might make it possible to recognise the

patients in whom coupling is deteriorating before the clear signs of pulmonary hypertension appear.

It would also be useful to compare the TAPSE/PAPs ratio with the indices built on the deformation of the ventricular wall, which in some series have shown greater prognostic ability (56,73), and to seek haemodynamic confirmation in patients with a reduced ratio, so as to establish what proportion of them actually has pulmonary hypertension.

These checks would have consequences for patient management. Treatment options in pulmonary hypertension associated with interstitial lung disease remain limited, since the drugs developed for pulmonary arterial hypertension have not produced results that can be transferred to this population, with the exception of inhaled treprostinil, studied in patients with pulmonary hypertension documented at catheterisation and considered by the European guidelines a class IIb option (25,76–78). Having a simple and repeatable index, sensitive to the early stages of uncoupling, would therefore be useful for selecting patients and for following their course over time.

The contribution of this work can be summarised in one point. In idiopathic pulmonary fibrosis, age at diagnosis is associated with a reduction in coupling between the right ventricle and the pulmonary circulation that does not emerge from the individual echocardiographic parameters or from pulmonary function tests, and that the TAPSE/PAPs ratio, obtainable from measurements already collected in everyday practice, makes recognisable.

8. CONCLUSIONS

The present study assessed, in 198 patients with idiopathic pulmonary fibrosis followed at a single centre, the relationship between age at diagnosis, pulmonary function, coupling between the right ventricle and the pulmonary circulation, and all-cause mortality. In the cohort there was no demonstrable cross-sectional association between age at diagnosis and the severity of respiratory impairment, although for DLCO a trend towards lower values in older patients remained.

The main finding is that older age at diagnosis is associated with a lower TAPSE/PAPs ratio, with a reduction of about 0.10 mm/mmHg for every ten years. The association was maintained in the models adjusted for sex, smoking habit and diffusing capacity, and it did not appear for TAPSE and PAPs considered separately.

What this work adds concerns the nature of this association. In patients with idiopathic pulmonary fibrosis, age at diagnosis is not accompanied by a generic right ventricular dysfunction, but by a reduction in coupling between the right ventricle and the pulmonary circulation, which the two parameters taken separately do not show and which pulmonary function alone does not allow to be predicted.

Age at diagnosis also proved relevant for survival, with a clearly higher probability of death in patients diagnosed at 65 years or older, corresponding to the band to which the GAP index assigns the maximum score for age. In the direct comparison between survivors and deceased patients, however, the two groups did not differ in age, whereas those who died had a worse cardiopulmonary profile. Their mean TAPSE/PAPs ratio fell within the range that the echocardiographic recommendations associate with uncoupling and with an increased risk.

DLCO was confirmed as the factor most firmly associated with pulmonary vascular involvement and with prognosis, while age was independently associated only with the coupling index. The two variables therefore carry partly distinct information, and the assessment of the right heart cannot be reduced to pulmonary function alone.

Clinically, these results point to a possible practical use. The TAPSE/PAPs ratio is obtained from two measurements already included in the echocardiographic assessment of the right side of the heart, without additional acquisitions, and

calculating it systematically in patients diagnosed after the age of 65 could help to identify those to be followed with more regular echocardiographic checks, even when pulmonary function is preserved.

Because of its observational and single-centre design, the study does not allow this indication to be turned into a recommendation. It does, however, provide a finding that is not so far described in this population and that, if confirmed in larger and prospective series, could help to define the timing and frequency of cardiological assessment in the patient with idiopathic pulmonary fibrosis.

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