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ORIGINAL ARTICLE

Cardiovascular Structural and Functional Parameters in Idiopathic Pulmonary Fibrosis at Disease Diagnosis

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Abstract

Introduction Prevalence of cardiac and vascular fibrosis in patients with Idiopathic Pulmonary Fibrosis (IPF) has not been extensively evaluated.

Aim In this study, we aimed to evaluate the heart and vessels functional and structural properties in patients with IPF compared to healthy controls. An exploratory analysis regarding disease severity in IPF patients has been done.

Methods We enrolled 50 patients with IPF (at disease diagnosis before antifibrotic therapy initiation) and 50 controls matched for age and gender. Heart was evaluated through echocardiography and plasmatic NT-pro-brain natriuretic peptide that, together with patients' symptoms, allow to define the presence of Heart Failure (HF) and diastolic dysfunction. Vessels were evaluated through Flow Mediated Dilation (FMD – endothelial function) and Pulse Wave Velocity (PWV—arterial stiffness)

Results Patients with IPF had a prevalence of diastolic disfunction of 83.8%, HF of 37.8% and vascular fibrosis of 76.6%. No statistically significant difference was observed in comparison to the control group who showed prevalence of diastolic disfunction, HF and vascular fibrosis of 67.3%, 24.5% and 84.8%, respectively. Disease severity seems not to affect PWV, FMD, diastolic dysfunction and HF.

Conclusions Patients with IPF early in the disease course do not present a significant CV fibrotic involvement when compared with age- and sex-matched controls. Bigger and adequately powered studies are needed to confirm our preliminary data and longitudinal studies are required in order to understand the time of appearance and progression rate of heart and vascular involvement in IPF subjects.

Keywords Idiopathic pulmonary fibrosis · Cardiac fibrosis · Vascular fibrosis · Heart failure · Arterial stiffness

1 Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic life-threatening fibrosing interstitial pneumonia of unknown cause [1]. Despite recently established anti-fibrotic treatment IPF prognosis is one of the worst among interstitial lung diseases characterized by an inexorable decline in lung function [2].

IPF is a complex disease associated with also various non-respiratory comorbidities. At the CardioVascular (CV) level ischemic heart disease, arrhythmias, pulmonary hypertension and heart failure can be found in patients with IPF [3, 4] but the mechanisms of these associations remain unclear.

Fibroproliferative process in various organ (including lung, heart and vessels) share common pathophysiological mechanisms (e.g. the activation of the transcription factor c-JUN, which causes uncontrolled production of collagen

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fibers by fibroblasts [5, 6]). Fibroblasts have a pivotal role in wound healing in response to organ injury. Following damage to the epithelium, fibroblasts are activated to proliferate locally and migrate to the sites of injury to rebuild the Extra-Cellular Matrix (ECM) scaffold for tissue repair. In fact, in IPF lung fibroblast senescence is increased and persistent with an excessive deposition of disorganized collagen and ECM, which result in the loss of normal lung architecture [7, 8].

One can speculate that the activation of similar pro-fibrotic pathways in the whole organism could lead to a high prevalence of cardiac and vascular fibrosis in IPF patients. However, studies on this topic are scanty particularly in patients that have been recently diagnosed and in which treatment have not yet been started.

So, our study was aimed at evaluate, with non-invasive methods such as Trans-Thoracic Echocardiography (TTE), NT-Pro-Brain Natriuretic Peptide (NT-pro-BNP), Flow Mediated Dilation (FMD) and Pulse Wave Velocity (PWV), the presence of cardiac and vascular fibrosis in patients with IPF at diagnosis comparing their values to the one of healthy controls. An exploratory analysis based on disease severity has also been performed in IPF patients.

2 Methods

2.1 Study Population and Design

In this observational study, we recruited 50 consecutive patients with an IPF diagnosis from the outpatient specialist clinic of San Gerardo Hospital (Monza, Italy), and 50 controls, recruited among hospital volunteers, matched for age (± 5 years) and gender.

Inclusion criteria were: IPF diagnosis according to the ATS/ERS/JRS/LATS 2018 guidelines [1] and antifibrotic treatment (either pirfenidone or nintedanib) not yet started.

Exclusion criteria were: active smoking, oxygen therapy at rest, presence of atrial fibrillation or flutter and limb amputation and/or severe peripheral vasculopathy (that doesn't permit to acquire PWV and FMD).

In IPF patients a respiratory evaluation was performed at the time of the diagnosis including Pulmonary Function Tests (PFTs), Diffusion Lung Carbon Onoxide (DLCO) and 6-Min Walking Test (6MWT). Control patients also underwent a pneumological visit to rule out chronic respiratory diseases. After the respiratory evaluation, both patients and controls underwent a cardiological visit at the Cardiology Unit of Niguarda Hospital, Milan, Italy. Here, TTE, NT-pro-BNP, FMD and PWV were performed.

Nt-ProBNP was quantified with an Electrochemiluminescence Immunoassay on Cobas e801 immunoassay analyser (Roche Diagnostics) at the Laboratory of Clinical Pathology of the Hospital Pio XI, Desio, Italy.

Vascular fibrosis was defined as a FMD < 4% or PWV > 10 cm/s [9, 10]. Similarly, Heart Failure with preserved Ejection Fraction (HFpEF) was defined, according to the 2021 European Society of Cardiology guidelines [11], as the presence of signs and symptoms of HF with an EF >50%, the presence of a NT-pro-BNP >125pg/mL and one of the following two criteria: i) presence of left ventricular hypertrophy or left atrial dilatation; ii) presence of diastolic dysfunction from 2nd to 4th grade.

2.2 Trans-Toracic Echocardiography

Two-dimensional (2D) echocardiograms were performed by an experienced cardiologist using a dedicated ultrasound machine (with an ultrasound transducer of 2.5 MHz) in each IPF patient and controls. 2D high frame rate gray-scale loops of four-chamber, two-chamber and three-chamber views with average frame rate of 50 frames per second (fps) were used in order to measure left ventricular end-diastolic diameter, interventricular septum and posterior wall thickness; left ventricular EF was evaluated using the Simpson method.

Left Ventricular Mass (LVM) was calculated using the Devereux formula [12]: LVM (g) = 0.8x1.04 x {[LVEDD (cm) + interventricular septum + posterior wall thickness (cm)]3-LVEDD3 (cm)}+0.6. LVM values were normalized for both BSA and $h^{2.7}$ to obtain the LVMI. We calculated BSA using the DuBois formula: BSA(m^2) = 0.007184 × height (cm)0.725 × weigh (kg)^0.425. LVH was diagnosed by the detection of a LVMI of at least 115 g/m^2 for men and at least 95 g/m^2 in women for BSA indexing [13].

Mitral diastolic inflow was interrogated using pulsed-wave Doppler from the apical 4-chamber view with the sample volume placed at the level of the mitral leaflet tips. Mitral early diastolic peak (E wave) and late peak (A wave) velocities, E/A ratio, and deceleration time of mitral early velocity were measured. Tissue Doppler (TD) was obtained at the apical 4-chamber view with the sample volume placed at the lateral mitral annulus. Early diastolic mitral annulus peak velocity (e′) was registered, and ratio of transmitral diastolic peak velocity to the mitral annular diastolic peak velocity (E/e′) was calculated.

Finally, right ventricle function was evaluated through tricuspid annular plane systolic excursion index and s' value with TD at the tricuspid level [14].

2.3 Flow Mediated Dilation

FMD of the brachial artery is an index of endothelium-dependent vasodilation and it has been widely used for assessment of endothelial function in humans because of its noninvasive nature, reflecting NO production in the

endothelium. FMD is estimated as the percentage increase in vessel diameter from baseline conditions to maximum vessel diameter during hyperaemia [15]. FMD ultrasound measurements of the brachial artery were performed according to relative guidelines [16, 17].

Using a high-resolution ultrasound (ESA-OTE MyLabα, Genova, Italy) with a 7.5 MHz linear array transducer, the measurements of the right brachial artery diameters were taken after supine rest for at least 10 min and after the complete deflation of the cuff performing the 5 minutes suprasystolic compression (50 mmHg above systolic pressure) of the right upper arm. A stereotactical arm was used for optimal transducer positioning on the brachial artery proximal of the bifurcation of the radial and ulnar arteries. The longitudinal image of the artery was recorded at baseline and immediately after cuff deflation. The baseline and maximum FMD diameters were measured from one media-adventitia interface to the other of the artery at end-diastole of the cardiac cycle with a real-time computerized edge detection system (Esaote, Genova, Italy) in order to obtain more precision and reproducibility. FMD of the brachial artery was estimated as the percent change in diameter over the baseline value.

In our laboratory the intra-session within- and between-operator variability of flow-mediated vasodilation are characterized by a coefficient of variation of the mean value amount to 8.5 and to 9.4%, respectively.

2.4 Pulse Wave Velocity

Aortic stiffness was evaluated by PWV between the carotid and the femoral artery of the same side with the patient in the supine position. The pressure pulse waveforms were simultaneously obtained at the two arterial sites on the right side using an automatic device (Complior, Colson; Alam Medical, Paris, France) and their distance calculated by taking the distance between hip and neck via a rigid ruler. Measurements were corrected by a 0.8 factor accordingly to the PWV measurement methods consensus documents which indicates the use of the subtraction methods instead of the direct one when assessing the distance between the two measurements points [18].

Two measurements were obtained in each patient and the mean was used for the analysis. In our laboratory the intra-session within- and between-operator variability of PWV amounted to a coefficient of variation, respectively, of the mean value of 2% and 4%. The corresponding value for the inter-session between-operator variability was 4%.

2.5 Statistical Analysis

Demographic characteristics, cardiovascular risk factors and comorbidities were summarized in patients with IPF and controls by quartiles and frequencies. Continuous variables are compared by the Mann-Whitney test, while categorical variables were compared by Chi-square or Fisher, as appropriate.

The association between the presence of cardiac and vascular fibrosis and the diagnosis of IPF was evaluated through a logistic regression model adjusting for the pairing variables (age and sex) and possible confounders that are: smoke and treatment with Angiotensin-converting enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARB). A second model with also systolic blood pressure and Heart Rate (HR) as covariates has been done. The magnitudes of the associations were presented as odds ratios with 95% confidence intervals.

An exploratory analysis based on the severity of IPF has been performed classifying patients on the "Gender, Age and Physiology" (GAP) index [19]. This score is commonly used by pulmonologists to evaluate IPF severity and is externally validated and correlates with 1-, 2- and 3-year mortality [20]. This score is based on gender, age and physiology that include FVC and DLCO. It classified patients into 3 stages (from I° stage: less severe, 1-year mortality risk 5.6%; to III° stage: more severe, 1-year mortality risk 39.2%). We divided the patients with IPF according to the GAP stage (I° stage 27-54%- patients and II°+III° stage 23-46%- patients, given the fact that patients in GAP III° stage were only 6-12%-) and evaluated the possible differences in the 4 outcomes of interest.

Type I error was set at 0.05 and R (https://cran.r-project.org/) was used for statistical analyses. This study received Ethics Committee approval and was registered on www.clinicaltrials.gov (NCT04177251).

3 Results

3.1 Populations Characteristics

Main clinical parameters recorded in patients with IPF and controls are summarized in Table 1. Overall, IPF patients were predominantly males (78%) and former smokers (72%) with a median [I–III quartiles] age of 74 [70-76] years.

No differences were seen for CV comorbidities regarding hypertension and valvular heart disease, while IPF patients presented higher prevalence of dyslipidemia (42 vs 26%, p = 0.139), diabetes mellitus (24 vs 14%, p = 0.308), obesity (6 vs 2%, p = 0.357), coronary artery disease (20 vs 8%, p = 0.161) and previous myocardial infarction (12 vs 6.1%, p = 0.487), although not significantly.

No significant differences were showed for hypertension duration while IPF patients present lower systolic (136 [120.2, 140.7] vs 146 [133, 156] mmHg, p = 0.002) blood pressure values with a borderline p-value for diastolic ones

Table 1 Baseline characteristics and cardiovascular parameters of patients with IPF and controls.

Variable	Controls	IPF Patients	P-value	Missing
n	50	50		
Demographic characteristics				
Male sex, n (%)	39 (78)	39 (78)	–	–
Age (years), median [I–III quartile]	72 [68, 76]	74 [70, 76]	–	–
GAP index: Grade I, n (%)	–	27 (54.0)	–	
Grade II, n (%)	–	17 (34.0)		–
Grade III, n (%)	–	6 (12.0)		
Cardiovascular risk factors				
Smoking history, never, n (%)	22 (45)	14 (28)	0.124	1
Prior, n (%)	27 (55)	36 (72)		
Pack/years, median [I–III quartile]	17 [10, 38]	30 [15, 40]	0.136	1
Hypertension, n (%)	25 (50)	24 (48)	1.000*	–
Hypertension duration (years), median [I–III quartile]	11.0 [9.0, 12.0]	8.5 [5.0, 19.5]	1.000	34
Dyslipidemia, n (%)	13 (26)	21 (42)	0.139	–
Diabetes mellitus, n (%)	7 (14)	12 (24)	0.308	–
Obesity, n (%)	1 (2)	3 (6)	0.357*	2
Cardiovascular comorbidities				
Valvular heart disease, n (%)	2 (4)	2 (4)	1.000*	1
Coronary artery disease, n (%)	4 (8)	10 (20)	0.161	1
Previous myocardial infarction, n (%)	3 (6)	6 (12)	0.487*	–
Previous atrial fibrillation, n (%)	0	1 (2)	1.000*	–
Heart failure, n (%)	0	1 (2)	1.000*	–
Peripheral Arterial Disease, n (%)	0	4 (8)	0.117*	–
Stroke, n (%)	1 (2)	0	1.000*	–
OSAS, n (%)	1 (2)	0	1.000*	–
Therapies for patients with hypertension (25 controls and 24 IPF patients)				
ACE Inhibitors, n (%)	2 (8)	11 (46)	0.008	–
ARB, n (%)	0	4 (16)	0.046*	–
Calcium Channel Blockers, n (%)	6 (33)	4 (17)	0.281*	7
Diuretics, n (%)	5 (28)	7 (29)	1.000	7
B-blockers, n (%)	7 (39)	11 (46)	0.893	7
Statins, n (%)	8(20)	21 (42)	0.055	11
Antiaggregant, n (%)	11 (28)	19 (38)	0.457	11
Cardiovascular parameters				
Systolic blood pressure (mmHg), median [I–III quartile]	146 [133, 156]	136 [120.2, 140.7]	0.002	17
Diastolic blood pressure (mmHg), median [I–III quartile]	84[79, 91]	79.5 [77, 84.7]	0.064	17
Heart rate (bpm), median [I–III quartile]	63 [58.5, 71.5]	73 [66, 80]	0.001	20
Ejection fraction (%), median [I–III quartile]	60 [59, 65]	60 [57, 61]	0.165	3
Left ventricular end diastolic diameter (mm), median [I–III quartile]	45.1 [40.1, 48]	41.7 [36.5, 46.8]	0.034	3
Left ventricular mass index (g/m2), median [I–III quartile]	84.8 [74.2, 94.7]	81.3 [60.1, 87.3]	0.071	30
Left ventricular hypertrophy (%), n (%)	3 (9)	1 (2)	0.315*	30
Relative wall thickness, median [I–III quartile]	0.44 [0.38, 0.48]	0.45 [0.40, 0.50]	0.237	3
Left atrial volume (mm3), median [I–III quartile]	39.3 [31.2, 47.1]	42.6 [33.9, 49.2]	0.349	14
Tricuspid Annular Plane Systolic Elevation (mm), median [I–III quartile]	22.2 [19.5, 25.2]	20.1 [18.3, 22.1]	0.003	14
Mean Pulmonary Arterial Pressure (mmHg), median [I–III quartile]	20.0 [15.0, 24.1]	19 [5, 28]	0.988	40
NT-pro-BNP (pg/ml), median [I–III quartile]	68.9 [37.6, 145.0]	95.5 [50.2, 166.0]	0.122	3
Diastolic Dysfunction, Normal, n (%)	13 (27)	6 (13)	0.134*	3
Grade I, n (%)	33 (67)	40 (83)		
Grade II, n (%)	3 (6)	1 (2)		
Grade III, n (%)	0	1 (2)		

Table 1 (continued)

Variable	Controls	IPF Patients	P-value	Missing
HFpEF, n (%)	12 (25)	17 (38)	0.242	6
PWV >10 cm/s, n (%)	35 (73)	31 (65)	0.509	4
FMD <4%, n (%)	9 (20)	13 (29)	0.427	9
Vascular Fibrosis (PWV >10cm/s and/or FMD <4%), n (%)	39 (85)	36 (77)	0.461	7
PWV (cm/s), median [I–III quartile]	11.55 [9.8, 13.1]	10.7 [9.8, 11.9]	0.087	4
FMD%, median [I–III quartile]	9.6 [5.5, 16.2]	8.00 [3.8, 17.0]	0.570	9

GERD Gastroesophageal reflux disease, *OSAS* Obstructive sleep apnea syndrome, *ACE* Angiotensin-converting enzyme, *ARB* Angiotensin Receptor Blockers, *HFpEF* heart failure with preserved ejection fraction, *PWV* Pulse wave velocity, *FMD* Flow mediated dilatation

*Fisher Exact Test

(79.5 [77, 84.7] vs 84 [79, 91] mmHg, p = 0.064). Also, HR was different with higher values observed in IPF patients (73 [66, 80 vs 63 [58.5, 71.5] mmHg, p = 0.001) when compared to controls.

Regarding anti-hypertensive drugs, the percentage of patients treated with ACE Inhibitors and ARBs was higher in IPF patients as compared to controls (26 vs 4%, p = 0.008 and 9 vs 0%, p = 0.046, respectively) without differences in other drug classes. A borderline p-value was seen for statins use (42 vs 20% for IPF and control respectively, p = 0.055) while no differences were found for antiaggregant therapies.

PFTs performed in patients with IPF showed a mild pulmonary impairment, with median FVC% 84% [I–III quartiles: 70, 99], median TLC% 72% [I–III quartiles: 62, 84], median DLCO% 51% [I–III quartiles: 39, 65], and median 405 [I–III quartiles: 360, 472.50] meters walked at 6MWT.

3.2 Heart and Vessels Involvement

Regarding echocardiographic data, IPF patients presented lower left ventricular end diastolic diameter (41.7 [36.5, 46.8] vs 45.1 [40.1, 48] mm, p = 0.034), while similar left ventricular mass index and left atrial volume values as well as left ventricular hypertrophy prevalence were observed. Neither patients nor controls had reduced EF whit similar median values (60 [59, 65] vs 60 [57, 61] % for control and IPF respectively, p = 0.165).

Data from the right ventricle showed a lower tricuspid annular plane systolic elevation value (20.1 [18.3, 22.1] vs 22.2 [19.5, 25.2] mm, p = 0.003) while mean pulmonary arterial pressure were similar between groups.

No significant differences were observed between IPF and control group in HFpEF (38 vs 25%, p = 0.242), diastolic dysfunction (grade I or higher, 88 vs 73%, p = 0.138) and vascular fibrosis (PWV >10 cm/s and/or FMD <4%; 77 *vs* 85%, p = 0.461). No differences were also seen for mean PWV (11.5 vs 10.7 m/s, p = 0.087) and FMD (9.6 vs 8%, p = 0.57) values in the two groups.

Figure 1 reports the results of the multivariable logistic regressions that did not shown an association between IPF and diastolic dysfunction (any grade versus normal, OR 2.24, 95% CI 0.63-9.27, p = 0.23), Pulse Wave Velocity (PWV>10 cm/s, OR 0.65, 95%CI 0.19-2.13), HFpEF (OR 1.02, 95%CI 0.28-3.54) and flow mediated dilatation (FMD <4%, 2.45 (95% CI 0.76-8.32, p = 0.14). Prior smoking history was associated with vascular fibrosis and age was associated with the presence of HfpEF and vascular fibrosis measure with PWV

A second model with also systolic blood pressure and HR as covariates has also been done without any significant changes in the results (supplementary figure 1).

3.3 IPF severity analyses

Data of IPF patients divided, accordingly to GAP stage, in less severe (GAP stage I) and more severe (GAP stage II and III) are shown in Supplementary Table 1. The latter are more frequently males (91 vs 67%) and, despite a similar prevalence of hypertension (56 vs 41%), had a longer disease duration (18 [10, 20] vs 5 [5, 7] years) and also a higher prevalence of diabetes mellitus (30 vs 18%).

IPF patients with GAP stage II and III had, when compared to stage I, a higher prevalence of coronary artery disease (39 vs 4%) and previous myocardial infarction (22 vs 4%) as well as peripheral artery disease (13 vs 4%).

They had lower systolic blood pressure values (118.5 [112.5, 137.5] vs 138.5 [129.5, 144.5] mmHg) and they were prescribed less frequently ACE-Inhibitors (38 vs 54%), but more frequently calcium channel blockers (31% vs 0).

No differences were found regarding echocardiographic data as well as for the outcomes of interest (diastolic dysfunction, PWV and FMD both as continuous or as categorical variables). A trend toward a lower prevalence of HFpEF in more severely affected IPF patients have been found (48 vs 75%) but without statistical significance also confirmed at multivariate analysis.

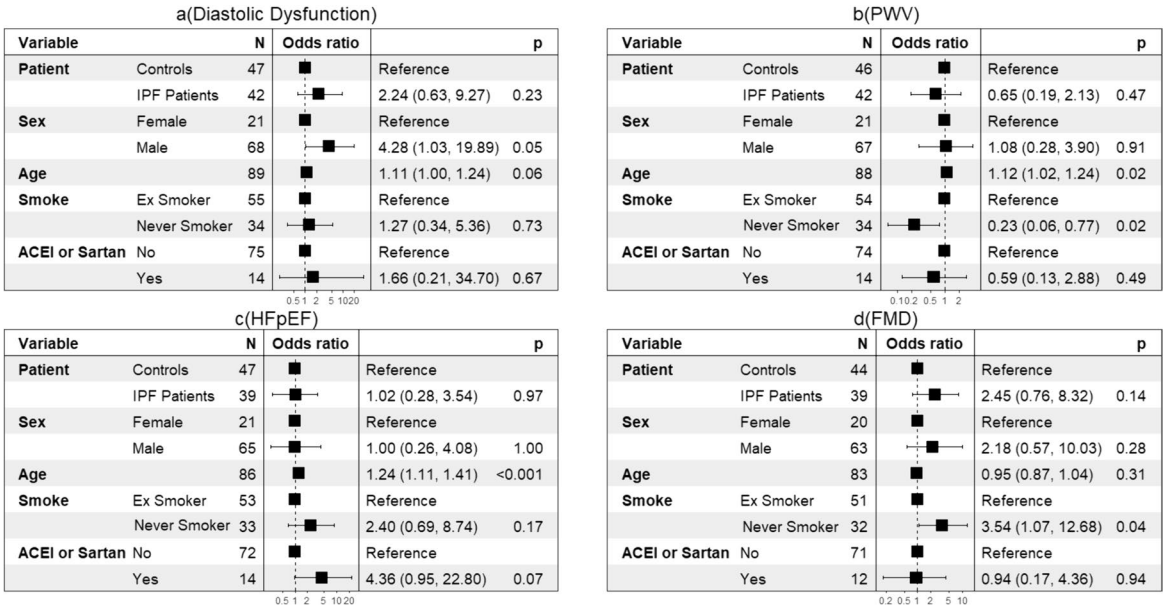

Fig. 1 Results of multivariable logistic regression models on the following outcomes: **a** Diastolic Dysfunction (any grade versus normal), **b** Pulse Wave Velocity (PWV > 10 cm/s), **c** Heart Failure with preserved ejection fraction (HFpEF) and **d** flow mediated dilatation (FMD < 4%). Results are graphically presented as Odds ratios and their 95% confidence interval and p-value, number of subjects in each group is also reported. *IPF* idiopathic pulmonary fibrosis, *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin Receptor Blockers, *HFpEF* heart failure with preserved ejection fraction, *PWV* Pulse wave velocity, *FMD* Flow mediated dilatation

4 Discussion

In our study we found that no heart (diastolic dysfunction and HFpEF) and vessels (endothelial function and arterial stiffness) fibrotic involvement was observed in patients with IPF when compared to an age- and sex-matched control cohort.

The hypothesis behind our study was that, being IPF a primary fibrotic disease and being pro-fibrotic cellular pathways similar in different organs, a concomitant fibrotic involvement of heart and vessels could be found these patients.

In fact, while the pathophysiology of chronic fibrotic disorders varies, there are three common mechanisms that are inflammation, oxidative stress and endothelial dysfunction.

Although fibrotic mechanisms in IPF are not completely understood, the main concepts of disease pathogenesis involve recurrent subclinical injuries to a genetically predisposed alveolar epithelium, followed by failure of alveolar re-epithelialization and repair. Activated cells within the alveoli release cytokines and growth factors that promote the recruitment, proliferation, and differentiation of lung fibroblasts into myofibroblasts, leading to excessive collagen deposition, progressive scarring of lung parenchyma, and irreversible loss of function [21] The current paradigm of IPF pathogenesis is focused on increased cell death, aberrant epithelial repair and dysregulated epithelial-fibroblast cross-talk promoting persistent mesenchymal activation and ECM deposition [22].

The complexity of IPF biology is demonstrated by the number of cell types and signalling pathways that have now been implicated in disease pathogenesis such as host defence, cell senescence, skewed immune responses including activation of macrophage subsets, fibroproliferative responses linked to aberrant kinase activation, transforming growth factor-β (TGF-β) and its downstream pro-fibrogenic pathways and developmental pathway reactivation [21, 23].

Multiorgan fibrotic involvement in patients with IPF have been evaluated only in few studies and mainly focused on hepatic [24] and CV involvement. Regarding the latter, prior studies found that patients with IPF may exhibit left ventricular fibrosis with a higher prevalence of diastolic dysfunction and an impairment in global longitudinal strain [25, 26]. Noteworthy, patients from these studies were in a more advanced stage of IPF compared to our cohort. In fact, FVC% was 70.3% [25] and 61% [26] while DLCO% was 35.8% [25] and 49% [26]. The same figures in our IPF cohort were 84 and 51%, respectively, indicating a less severe disease, determined by the fact that they were enrolled directly at IPF diagnosis and prior to antifibrotic therapy initiation or oxygen supplementation. This was not the case for the study by Sonaglioni et al., in which patients were enrolled in a stable phase, but 84% of them was on antifibrotic therapies and 62% received oxygen supplementation [25]. No data were

shown regarding specific therapies for IPF in the study by Papadopoulos et al. [26].

Arterial elastance index, a non-invasive marker of arterial stiffness but, differently from PWV, not the gold standard for this evaluation, was found significantly increased in patients with IPF compared to controls [27]. Again, those patients showed a more advanced stage of the disease according to PFTs (FVC% 70% and DLCO% 37%) and therapies (79.3% on antifibrotic and 65% on oxygen supplementation).

For instance, in the study of Papadopoulos et al. [26], it was hypothesised that, apart from right ventricular (RV) dysfunction, patients with IPF also exhibit left ventricular (LV) impairment, which may affect disease progression and prognosis. Notably IPF patients exhibited mild-to-moderate pulmonary arterial hypertension reflecting a more advanced stage of the disease. In addition to the expected impairment in RV function, all patients showed a characteristic reversal of LV diastolic filling to late diastole compared with controls and they also exhibited lower peak myocardial velocities in early diastole, higher in late diastole, lower Em/Am ratio and higher E/Em ratio, all indicative of LV diastolic dysfunction. Moreover, LV propagation velocity was significantly lower in IPF patients. Therefore, it was demonstrated that patients with clinically stable IPF exhibit not only RV diastolic and systolic dysfunction but also impaired LV diastolic filling. Conversely, LV systolic function seems to be preserved.

In another study by D'Andrea et al. conducted in stable (but not recently diagnosed) IPF patients it has been found that RV myocardial dysfunction is present at rest and worsens during exertion as detected by two-dimensional speckle-tracking echocardiography [28].

Despite the absence of a significant difference between groups and association at multivariate analysis we observed some trends that may be also useful for future studies. A trend for a better vascular function (lower PWV and FMD) and for a worst heart function (higher NT-pro-BNP, higher prevalence of diastolic disfunction and HFpEF) were found in IPF patients. A factor that could, at least in part, explain the differences in vascular function is the higher use of ACE Inhibitors and ARB in this population. In fact, these two farmacological classes have a positive effects on PWV and FMD [29–32]. Similarly, also the higher systolic blood pressure (well known as the main determinant of PWV [33]) and the lower HR [34] observed in the control group may act as a substantial confounding factors. However, we inserted all these variables into the multivariate models without substantial changes in the results. Regarding the cardiac function, it is possible that our sample size and the early stage of the pulmonary fibrotic disease did not allow us to appreciate a significant increase in the prevalence of HFpEF.

In the exploratory analysis based on disease severity (defined using the GAP score) there were no significant findings. However, the subgroup analysis had only few patients (27 vs 23) and further studies adequately powered are needed on this specific point.

To the best of our knowledge, this is the first study assessing the prevalence of heart and vessels fibrosis in a cohort of IPF patients immediately after the diagnosis and before they started antifibrotic therapies. The fact that we enroll newly diagnosed and never treated subjects is of particular importance and probably drives our results to the absence of significant differences compared to controls. Although patients with IPF may often experience a diagnostic delay, the cardiac and vascular alterations could appear later in the disease course. Longitudinal studies are needed in order to understand the time of appearance and progression rate of heart and vascular involvement in IPF subjects. The results of our study can constitute the base on which other studies can be planned to answer to these open questions. Such a kind of study has been already planned in our centre (CARDIO-IPF-2).

Our study presents some limitations. First of all, the small sample size, partially due to the delay in recruitment and premature termination determined by the COVID-19 pandemic, that reduces our power to detect important associations or findings. In fact, based on the observed data on FMD (20% of controls with FMD<4%) we had only a 53% power to detect an odds ratio of 2.5, while the study was sized to detect a stronger association (82% power to detect an odds ratio of 3.5). As far as Diastolic Dysfunction (73% in control subjects) the post-hoc power is 42% and 62% to detect an odds ratio of 2.5 and 3.5, respectively. Secondly, a more accurate evaluation of CV fibrosis through other non-invasive techniques are missing at the moment. Probably magnetic resonance imaging and speckle tracking echocardiographic technique could have provided interesting additional information. In fact, cardiac magnetic resonance with late gadolinium enhancement is currently recognized as the gold standard for the detection of focal and diffuse cardiac chambers myocardial fibrosis [35]. However, its use is limited by the availability of this methodology and the use of contrast agents. Similarly, advanced echocardiographic techniques, above all speckle-tracking echocardiography, proved to be highly reliable for early detection of structural myocardial abnormalities and for the prediction of prognosis in acute and chronic HF. Myocardial strain of both ventricles and also left atrium has been shown to correlate with the degree of myocardial fibrosis, providing useful prognostic information in several diseases, such as HF, cardiomyopathies and valvular heart disease [36].

Thirdly, further biomarker analyses could help to better clarify the pro-fibrotic mechanisms with multi-organ involvement. The transformation of cardiac fibroblast to cardiac myofibroblast is suspected to play a vital part in the development of HF and could be evaluated through various biomarkers such as renin and angiotensin [37],

vimentin, discoidin domain receptor 2, α-smooth muscle actin and TGF-β1 [38].

In conclusions, patients with IPF early in the disease course do not present a significant CV fibrotic involvement when compared with age- and sex-matched controls. Bigger and adequately powered studies are needed to confirm our preliminary data and longitudinal studies are required in order to understand the time of appearance and progression rate of heart and vascular involvement in IPF subjects.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40292-024-00638-0.

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Declarations

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Conflict of interest Authors have no conflict of interest to declare

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