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Subclinical liver fibrosis in patients with idiopathic pulmonary fibrosis / Cocconcelli, E; Tonelli, R; Abbati, G; Marchioni, A; Castaniere, I; Pelizzaro, F; Russo, Fp; Vegetti, A; Balestro, E; Pietrangelo, A; Richeldi, L; Luppi, F; Spagnolo, P; Clini, E; Cerri, S.. - In: INTERNAL AND EMERGENCY MEDICINE. - ISSN 1970-9366. - 16:2(2021), pp. 349-357. [10.1007/s11739-020-02376-2]

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24/07/2024 12:07

Internal and Emergency Medicine Subclinical liver fibrosis in patients with idiopathic pulmonary fibrosis --Manuscript Draft--

Manuscript Number:	IAEM-D-20-00198	
Full Title:	Subclinical liver fibrosis in patients with idiopathic pulmonary fibrosis	
Article Type:	ORIGINAL	
Section/Category:	IM - ORIGINAL	
Keywords:	lung fibrosis, liver fibrosis, hepatic transient elastography	
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Abstract:	Background - Data on the presence of subclinical fibrosis across multiple organs in patients with idiopathic lung fibrosis (IPF) are lacking. Our study aimed at investigating through hepatic transient elastography (HTE) the prevalence and clinical impact of subclinical liver fibrosis in a cohort of patients with IPF. Methods - Patients referred to the Centre for Rare Lung Disease of the University Hospital of Modena (Italy) from March 2012 to February 2013with established diagnosis of IPF and without a documented history of liver diseases were consecutively enrolled and underwent HTE. Based on hepatic stiffness status as assessed through METAVIR score patients were categorized as " with liver fibrosis "	

	(corresponding to a METAVIR score of F1-F4) and " without liver fibrosis" (METAVIR F0). Potential predictors of liver fibrosis were investigated through logistic regression model among clinical and serological variables. The overall survival (OS) was assessed according to liver fibrosis and multivariate Cox regression analysis was used to identify independent predictors. Results - In 13 out of 37 patients (35%) with IPF a certain degree of liver fibrosis was documented.No correlation was found between liver stiffness and clinical-functional parameters. OS was lower in patients ' with liver fibrosis' than in patients ' without liver fibrosis' (median months 33[23-55] vs. 63[26-94], p=0.038). Patients ' with liver fibrosis' presented a higher risk of death at seven years as compared to patients ' without liver fibrosis' (HR=2.6, 95%CI[1.003–6.7],p= 0.049). Higher level of AST to platelet ratio Index (APRI)was an independent predictor of survival (HR=4.52 95%CI[1.3–15.6], p=0.02). Conclusions - In our cohort, more than one third of IPF patients had concomitant subclinical liver fibrosis that negatively affected OS. These preliminary claims further investigation aimed at clarifying the mechanisms beyond multiorgan fibrosis and its clinical implication in patients with IPF.
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Subclinical liver fibrosis in patients with idiopathic pulmonary fibrosis

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Abbreviations list

 BMI – Body Mass Index; TLC – Total Lung Capacity; FVC – Forced Vital Capacity; DLCO – Diffuse Lung Capacity for Carbon Dioxide; GAP – Gender, Age, P pulmonary function (FVC, DLCO); PBC - primary biliary cirrhosis; PSC - and primary sclerosing cholangitis; AMA - antimitochondrial antibody; ASMA - anti-smooth muscle antibodies; AST - aspartate aminotransferase; ALT - alanine aminostransferase; γGT - gamma-glutamyl transpherase; IgG4 - immunoglobulin G4; APRI - AST to platelet ratio Index.

Abstract

Background

Data on the presence of subclinical fibrosis across multiple organs in patients with idiopathic lung fibrosis (IPF) are lacking. Our study aimed at investigating through hepatic transient elastography (HTE) the prevalence and clinical impact of subclinical liver fibrosis in a cohort of patients with IPF.

Methods

Patients referred to the Centre for Rare Lung Disease of the University Hospital of Modena (Italy) from March 2012 to February 2013 with established diagnosis of IPF and without a documented history of liver diseases were consecutively enrolled and underwent HTE. Based on hepatic stiffness status as assessed through METAVIR score patients were categorized as *"with liver fibrosis"* (corresponding to a METAVIR score of F1-F4) and *"without liver fibrosis"* (METAVIR F0). Potential predictors of liver fibrosis were investigated through logistic regression model among clinical and serological variables. The overall survival (OS) was assessed according to liver fibrosis and multivariate Cox regression analysis was used to identify independent predictors.

Results

In 13 out of 37 patients (35%) with IPF a certain degree of liver fibrosis was documented. No correlation was found between liver stiffness and clinical-functional parameters. OS was lower in patients '*with liver fibrosis*' than in patients '*without liver fibrosis*' (median months 33[23-55] vs. 63[26-94], p=0.038). Patients '*with liver fibrosis*' presented a higher risk of death at seven years as compared to patients '*without liver fibrosis*' (HR=2.6, 95%CI[1.003–6.7],p= 0.049). Higher level of AST to platelet ratio Index (APRI) was an independent predictor of survival (HR=4.52 95%CI[1.3–15.6], p=0.02).

Conclusions

In our cohort, more than one third of IPF patients had concomitant subclinical liver fibrosis that negatively affected OS. These preliminary claims further investigation aimed at clarifying the mechanisms beyond multiorgan fibrosis and its clinical implication in patients with IPF.

Background

Fibrogenesis is a key mechanism of tissue repair representing a physiological response to injury (1). In some pathological conditions, however, this pathway may result dysregulated so that undue fibroproliferation and extracellular matrix deposition occur, leading to tissue injury and dysfunction (2). Every tissue or organ may potentially be involved. While tissue specific injury has different origin, responses to injury and repair mechanisms are similar across different organs (3). Many distinct causes can contribute to the development of progressive fibrotic diseases, including genetic abnormalities, infections, exposure to toxins or pollutants, micro-aspiration of gastric content, tobacco smoke, chronic autoimmune inflammation (4).

In idiopathic pulmonary fibrosis (IPF), a specific form of chronic and progressive interstitial pneumonia, repeated subclinical damages to alveolar epithelial cells (AECs) superimposed on accelerated epithelial aging lead to abnormal healing processes and deposition of interstitial fibrosis by fibroblasts and myofibroblasts (5,6). IPF represents a particularly arduous challenge, as, in contrast to other forms of lung injury, knowledge about the inciting injury, progressive fibroproliferation and lack of resolution are only partially understood (6-8). Consequently, there are no therapies able to halt or reverse the fibrotic process of IPF.

Whether the activation of a fibrotic response in one organ might induce similar manifestations in other organs, as a result of the activation of common pathways, is unknown. Specifically, robust data about the co-existing presence of fibrotic disease across multiple organs in patients with IPF are lacking. With this background, the aim of our study is to evaluate the prevalence and clinical relevance of subclinical hepatic fibrosis through hepatic transient elastography (HTE) in patients diagnosed with IPF without clinically overt liver disease.

Materials and methods

Study population

We consecutively enrolled patients with established diagnosis of IPF referred to the Centre for Rare Lung Diseases of the University Hospital of Modena (Italy) over a 12-month period (from March 2012 to February 2013). Demographic, clinical and functional data (forced vital capacity [FVC] and diffusing capacity of the lung for carbon monoxide [DLCO]) were recorded at the time of diagnosis. Each patient started antifibrotic treatment (either pirfenidone or nintedanib) at diagnosis. Disease severity score of IPF patients was recorded using the GAP-staging system, which includes gender, age, FVC and DLCO (9).

The exclusion criteria were: documented history of chronic liver disease of known cause; positive screening for potential secondary causes of liver fibrosis including positive serology for chronic hepatitis B or C virus infection, history of alcohol abuse (> 2 units of alcohol), pharmacological treatments with prevalent hepatic metabolism, body mass index (BMI) > 29 kg/m², inability to express a valid informed consent.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital of Modena (Prot n. 2645). Informed consent was obtained for all study participants.

Liver stiffness evaluation

HTE was performed using Fibroscan[®] (Echosense[™], Paris, France) at the Hereditary and Metabolic Center for Liver Diseases of the University Hospital of Modena. The exam was performed by internal medicine physicians experienced in hepatic fibrosis who were blinded to the past medical history of each patient and to the design of the study. HTE was performed with patient lying flat on the back, with the right arm tucked behind the head to facilitate the access to the hepatic right lobe. The tip of the probe transducer was placed on the skin between the rib bones at the level of the right hepatic lobe. Once the measurement area had been located, signal acquisition was started. The Fibroscan[®] internal software (Echosense[™], Paris, France) determined whether each measurement was successful or not. The overall liver stiffness corresponded to a mean of 10 successful measurements and was expressed in kiloPascals (kPa). Liver stiffness values ranged from 2.5 to 75 kPa and were immediately available and operator-independent (10). Liver kPa stiffness threshold values were related to METAVIR parameters. In particular values range 0 - 5.2 kPa corresponded to METAVIR F0 (absence of fibrosis), range 5.3 kPa - 7.4 kPa to METAVIR F1 (fibrosis exist with expansion of portal zones – mild fibrosis), range 7.5 kPa-9 kPa to METAVIR F2 (fibrosis exist with expansion of most portal zones and occasional bridging – significant fibrosis), range 9.1 kPa - 13.1 kPa to METAVIR F3 (fibrosis exist with expansion of most portal zones and occasional bridging – significant fibrosis) respectively (11).

Based on METAVIR parameters, IPF patients were categorized as *'with liver fibrosis'* (if METAVIR value correspond to F1, F2, F3, F4) or *'without liver fibrosis* (if METAVIR value correspond to F0). All patients enrolled in the study were further investigated for liver disease. These investigations included autoantibodies for the autoimmune hepatitis, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) (anti-nuclear antibodies [ANA], anti-Liver and Kidney Microsomes [anti-LKM] antibodies, antimitochondrial antibodies [AMA], anti-smooth muscle antibodies [ASMA]), serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT), bilirubin, iron, and circulating immunoglobulins G4 (IgG4). The AST to platelet ratio Index (APRI), a predictor of liver fibrosis, was calculated as follows: AST/upper limit of normal x 100/platelet count (12,13).

Statistical analysis

Categorical variables are expressed as absolute (n) and relative values (%) whereas continuous variables as median and interquartile range (IQR). To compare demographic data and baseline clinical characteristics between IPF patients *'with liver fibrosis'* and IPF patients *'without liver fibrosis'*. Chi square test and Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables were used, as appropriate.

The correlation between liver stiffness values in kPa and each serum parameter was assessed for the entire study population and in the two groups of IPF patients (with liver fibrosis and without liver fibrosis) with the nonparametric Spearman's rank method. Univariate logistic regression analysis was performed to detect predictors of liver fibrosis.

The overall survival (OS) was calculated from diagnosis to death or lung transplantation, with data censured at September 1st, 2019. The cumulative survival rate was calculated using Kaplan-Meier method and the difference in the survival time between the two groups (*'with liver fibrosis'* and *'without liver fibrosis'*) was assessed with log-rank test. A multivariate Cox regression analysis was used to determine which clinical and serological features were independently associated with survival. Only variables with a statistically significant and almost significant (0.05 < p < 0.09) association with OS at the univariate analysis were included in the multivariate model.

All data were analysed using SPSS Software version 25.0 (New York, NY, US: IBM Corp. USA). P-values < 0.05 were considered statistically significant. The statistical package GraphPad Prism 7.0 (GraphPad Software, Inc. La Jolla, CA, USA) was used for graphs.

Results

Forty-eight consecutive IPF patients were considered and 37 were finally enrolled in the study (Table 1). In 29 patients (78%), HTE measurements for liver stiffness were considered reliable while for 8 patients (22%) HTE measurements were unsuccessful as the software could not determine a final mean measurement of liver stiffness from ten valid measurements. Sixteen out of the 29 patients (55%) had a median liver stiffness value of 3.65 kPa (range, 2.60 - 5.10 kPa) corresponding to a METAVIR value of FO and were classified as 'without liver fibrosis'. Four patients had a median liver stiffness of 6.70 kPa (6.10 - 7.40 kPa) corresponding to a METAVIR value of F1, six patients had a median liver stiffness of 7.70 kPa (7.60 - 8.40 kPa) corresponding to a METAVIR value of F2, one patient had a liver stiffness value of 9.50 kPa corresponding to a METAVIR value of F3 and two patients had a liver stiffness value of 14.30 and 45.30 kPa corresponding to a METAVIR value of F4. Patients with liver stiffness corresponding to a METAVIR value of F1-F2-F3-F4 formed the group of IPF patients 'with liver fibrosis' (Figure 1). Demographics and functional data of the 29 patients evaluated for liver stiffness are presented in Table 2. Patients 'with liver fibrosis' present lower age at diagnosis as compared to patients 'without liver fibrosis' (66 years [54-78] vs. 75 years [42-83] respectively; p = 0.04], but the two groups were similar with regard to the demographic features (sex, smoking history, radiological diagnosis) as well as functional parameters (FVC, DLCO, GAP score) (Figure 1).

Serum analysis and correlations

Blood tests (AST, ALT, γGT, platelets, total bilirubin, APRI index, IgG4, iron, ferritin and transferrin) were similar in patients '*with liver fibrosis*' and '*without liver fibrosis*' (Table 2). Notably, one of the two patients with F4 on HTE measurements had also high IgG4 levels (i.e. 419 mg/dL; normal values defined as lower than 86 mg/dL) and underwent liver biopsy, which revealed chronic idiopathic liver disease. No correlation between liver stiffness values (kPa) and clinical-functional parameters (age,

smoking history, FVC, DLCO, GAP score) or blood tests (AST, ALT, γ GT, APRI index, IgG4, ferritin and transferrin) was found, neither in the entire study population of IPF patients evaluated for liver fibrosis nor when it was stratified by presence/absence of liver fibrosis. Gender, functional data at baseline, APRI test, and AST/ALT/ γ GT were not associated with liver stiffness at univariate logistic regression (Table 3).

Survival analysis

Survival was estimates during a follow up time of 7 years, with median OS of 44 months. The OS of patients '*with liver fibrosis*' was lower than patients '*without liver fibrosis*', with a median OS of 33 (23-55) months for patient '*with liver fibrosis*' and 63 (26-94) months for patients '*without liver fibrosis*' (*p=0.038*) (*Figure 2*). Patients with liver fibrosis presented higher risk of death at seven years as compared to patients without hepatic involvement (HR 2.6, 95% CI 1.003 – 6.7; p= 0.049, Figure 2) (Figure 3).

Univariate analysis of factors associated with survival revealed that lower DLCO at diagnosis, GAP score III compared to GAP score I, presence of liver fibrosis and high levels of APRI score had a significant negative association with survival in the whole IPF population (Table 4). Multivariate analysis showed that only high level of APRI was an independent predictor of survival in our IPF cohort (HR: 4.52 95%CI [1.3 – 15.6]; p = 0.02).

Discussion

 Our study aimed at non-invasively assessing whether IPF patients without a clinical overt liver disease may present subclinical hepatic fibrosis. We found that IPF patients presented a significant prevalence of liver fibrosis (35%) that negatively affected survival.

To our knowledge, robust evidences about the co-existing presence of fibrotic disease across multiple organs in patients with IPF are lacking. Collagen deposition is an indispensable and typically reversible part of wound healing, even though normal tissue repair can evolve into a progressive and irreversible fibrotic response when tissue injury is severe or if the wound-healing response results dysregulated (1,2,14). A feature shared by all fibrotic diseases is the activation and differentiation of fibroblasts into myofibroblasts, which are specialized contractile cells with higher profibrotic potential than fibroblasts. Within the fibroblastic foci, which define the histological usual interstitial pneumonia (UIP) pattern of lung fibrosis observed in IPF, myofibroblasts cause exaggerated extracellular matrix (ECM) deposit, that is the hallmark of the scarring process (14). Pathological liver fibrosis is similarly characterized by excessive accumulation of ECM proteins, (fibrillar collagens, glycoproteins and proteoglycans) and is induced by activated myofibroblasts

(15). Bridging fibrosis and regeneration nodes are the clearest manifestation of this injury, being cirrhosis the end stage of this process (16). Excessive collagen deposition distorts the normal liver tissue architecture, leading to hepatocellular dysfunction and increased hepatic resistance to blood flow, which cause hepatic insufficiency and portal hypertension (17,18).

Our data show that more than one third of IPF patients have a concomitant and clinically unremarkable fibrosing process in the liver. Having excluded subjects with potentially secondary causes for liver diseases, our IPF cohorts seems to be affected by an idiopathic/cryptogenic liver fibrosis. At baseline, IPF patients '*with*' and '*without liver fibrosis*' are homogeneous in terms of clinical and functional data as well as serological tests. Of interest, patients '*with liver fibrosis*' gain

the diagnosis of IPF younger as compared to patients '*without liver fibrosis*', maybe because the systemic involvement leads to an earlier onset of symptoms and disease awareness. Two examples of potential common pathways responsible for fibrotic processes occurring in different organs were proposed in the past: 1) Excessive telomere shortening, as a consequence of telomerase gene mutations, ultimately leading to apoptosis and organ failure, specifically in the lung, but also in the liver; 2) Germ-line mutations in telomerase components hTERT and hTR, that are found in a subset (8-15%) of patients with familial pulmonary fibrosis (19,20). Moreover, as compared with agematched controls, patients with IPF have shorter telomeres regardless of whether they carry telomerase-related mutations (21,22). In the liver, excessive telomere shortening, as a consequence of telomerase to chronic damage, thus facilitating fibrosis progression.

Although percutaneous biopsy has traditionally been considered as the gold standard for the diagnosis and staging of chronic liver diseases, researchers have invested much efforts to develop noninvasive tests able to evaluate liver fibrosis.

Both instrumental and serological methods to evaluate liver fibrosis were developed and validated (10,23-28). Among these, HTE has been evaluated as a non-invasive method for assessing liver fibrosis in a variety of chronic liver diseases while APRI is a simple index calculated with readily available laboratory results that proved to identify with a high degree of accuracy the presence of significant fibrosis and cirrhosis in patients with chronic HCV-related hepatitis (28). The mean liver stiffness value discovered in healthy patients without overt causes of liver disease and normal liver enzymes, has been estimated 5.5 ± 1.6 kPa. Age has no influence, but liver stiffness values have been found higher in obese patients and males (10). Liver stiffness assessment can be difficult in patients with BMI > 29 and in those with narrow intercostal space and cannot be performed in patients with ascites. According to experienced reported measurements, liver stiffness cannot be

measured in 5-15% of cases (24-27). In our study we have observed a greater proportion of unreliable measurements (22%) mainly due to either increased thickness of subcutaneous adipose tissue of the chest (n=6) or narrow intercostal spaces (n=2).

Of great interest, our data showed that patients '*with liver fibrosis*' have a shorter survival as compared to patients '*without liver fibrosis*' (median survival of 33 vs. 63 months, respectively). The worst prognosis of patients with subclinical liver fibrosis opens an intriguing scenario, in the context of a disease, like IPF, universally considered as being limited to the lungs.

These preliminary data may indicate the usefulness of a systemic approach to clarify the possible correlation between the fibrotic process across lung and liver. More focused studies are needed to identify cellular/molecular pathways of response to injury - if any - that are shared by liver and lung fibrosis. Detection of a subgroup of patients with idiopathic fibrotic disease involving more organs, would allow the definition of a new clinical phenotype, paving the way for future research. Future studies may also analyze whether short telomeres may contribute to such phenotype.

If common pathogenetic mechanisms between lung and liver fibrosis are identified, this would inevitably impact on prognosis and treatment of IPF. Indeed, concomitant liver fibrosis may potentially influence response of IPF patients to antifibrotic drugs and may explain, at least in part, the variable degrees of functional decline and disease progression observed in both clinical trials and real-word studies of pirfenidone and nintedanib. Moreover, concomitant liver fibrosis may increase patient susceptibility to liver toxicity, which is one of the most common side effects of antifibrotic therapy.

In our population, we finally analyzed which indicators could be independent predictors of survival. Our data revealed that only lower levels of APRI is an independent predictor of survival in IPF patients (HR: 4.52; 95%CI: 1.30 - 15.6; p = 0.02), which is added to the predictive role of liver fibrosis.

The findings of our study should be seen in light of some limitations. First of all, our study did not include an age-matched control group. Secondly the study population is relatively small; however, IPF is a rare disease, and collecting a large number of patients is challenging. Thirdly, patients with BMI > 29 (n=6) were excluded due to the intrinsic limitation of the HTE technique while 5 patients were excluded based on their morphotype. As a result, our findings need to be further confirmed before being generalizable to the broader population of IPF patients.

In conclusion, our study shows that a relevant proportion of patients with IPF have also liver fibrosis; whether the co-existence of the two conditions is caused by common fibrogenic pathways needs to be explored further. In particular, this subset of IPF patients should be investigated for carriage of telomerase mutations and telomere length. IPF has long been considered the prototypic disease limited to the lung. However, if confirmed by larger studies, our data suggest that, at least in a subset of patients, IPF may be part of multiorgan fibrotic phenotype.

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Figure legend

Figure 1

Parts of the whole population enrolled in the study. Grey box indicates patients with not reliable Fibroscan[®] measurements, light green box indicates patients without liver fibrosis and dark green box indicates patients with liver fibrosis.

Figure 2

Survival curves of IPF patients according to the presence of liver fibrosis.

Figure 3

Cumulative average survival time of IPF patients according to the presence of liver fibrosis.

Declarations

Ethics approval and consent to participate

Approval from the local ethics committee of Modena was obtained (registered protocol n. 2645). Written informed consent to participate was obtained from all patients enrolled or their relatives, when appropriate.

Consent for publication

Consent for publication was obtained from all patients enrolled.

Availability of data and materials

Data are available at the Respiratory Disease Unit of the University Hospital of Modena, Italy.

Funding

None.

Competing interests

The authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

Authors contributions

EC and RT made substantial contribution to the concept, design, conduction of the study and to the realization of the manuscript, thus they ought to be considered both as first author.EC, RT, SC and LR designed the study, enrolled patients and wrote the paper. GA, IC, FP and EB made substantial contributions to literature review, data collection and paper writing. AV, FPR, FL and AM reviewed the literature, wrote the manuscript and produced the figures. AP critically reviewed and edited the manuscript. PS, LR and EC designed the study and reviewed and edited the manuscript. All the authors made substantial contribution to the realization of the work and approved the final version of the manuscript.

Acknowledgments

We want to thanks Professional Editor Colin Woodham for language editing.



with liver fibrosis, n=13 (35%)
 without liver fibrosis, n= 16 (43%)

not reliable measurements, n = 8 (22%)

Total n = 37





Patients without liver fibrosis

Patients with liver fibrosis

Variable	
Patients – n (%)	37 (100)
Male – n (%)	26 (70)
Female – n (%)	11 (30)
Age at diagnosis – years	71 (42–83)
Smoking history – pack/years	10 (0-64)
Clinical-radiological diagnosis – n (%)	28 (76)
Histological diagnosis – n (%)	9 (24)
FVC at diagnosis – %pred.	78 (22–120)
DL _{co} at diagnosis – %pred.	36 (11–102)
Gap score	
I	14 (38)
Ш	16 (43)
III	7 (19)

Table 1

Baseline characteristics of 37 IPF patients included in the study.

Variable	Population	Without liver	With liver fibrosis	
Male – <i>n (%)</i>	21 (72)	10 (62)	11 (85)	0.23
Female – <i>n (%)</i>	8 (28)	6 (38)	2 (15)	
Age at diagnosis –	71 (42–83)	75 (42-83)	66 (54-78)	0.04
Smoking history –	10 (0-64)	3 (0-64)	21 (0-45)	0.42
Radiological	22 (76)	13 (81)	9 (69)	0.66
Histological	7 (24)	3 (19)	4 (31)	
FVC at diagnosis –	78 (22–120)	72 (22-120)	79 (45-98)	0.34
DL _{co} at diagnosis –	35 (11–102)	38 (11-65)	35 (23-102)	0.80
GAP score				
I	11 (38)	5 (31)	6 (46)	
Ш	14 (48)	9 (56)	5 (39)	0.62
ш	4 (14)	2 (13)	2 (15)	
Liver stiffness – <i>kPa</i>	4.50 (2.60-45.30)	3.65 (2.60-5.10)	7.60 (6.10-45.30)	< 0.0001
APRI index	0.23 (0.16-1.24)	0.25 (0.17-0.51)	0.23 (0.16-1.24)	0.78
Platelets – n x10 ⁹ /L	250 (156-363)	251 (157-363)	236 (156-324)	0.37
AST – U/L	20 (13-82)	20 (15-27)	22 (13-82)	0.86
ALT – U/L	15 (8-80)	14 (8-29)	28 (8-80)	0.10
γGT – U/L	21 (12-643)	20 (12-42)	42 (12-643)	0.14
Bilirubin total –	0.43 (0.24-1.45)	0.40 (0.26-0.65)	0.51 (0.24-1.45)	0.23
lgG 4 – mg/dL	52 (10-618)	52 (23-618)	96 (10-433)	0.88
Iron – umol/l	91 (19-175)	104 (86-139)	78 (19-175)	0.18
Ferritin – ug/l	99 (22-276)	92 (22-276)	135 (59-227)	0.93
Transferrin – g/L	357 (258-522)	335 (258-399)	379 (275-522)	0.48

Table 2

Baseline characteristics of the 29 IPF patients evaluated for liver stiffness, of which 16 without liver fibrosis on HTE measurements and 13 with liver fibrosis. Data are presented as number and percentage for dichotomous values or median and ranges for continuous values.

		Univariate analy	sis
		OR (95% CI)	p Value
Gender	Female	Ref.	
	Male	3.30 (0.60 - 26.26)	0.19
Age at diagnosis		0.95 (0.86 - 1.02)	0.17
FVC at diagnosis - % pred.	> 80	Ref.	
	60 - 80	0.14 (0.006 – 1.25)	0.11
	< 60	0.59 (0.10 – 3.08)	0.53
DL _{co} at diagnosis - % pred.	> 50	Ref.	
	35 -50	0.66 (0.067 - 5.53)	0.70
	< 35	0.33 (0.03 - 2.8)	0.31
GAP score	I	Ref.	
	П	1.2 (0.11 to 13.3)	0.87
	ш	0.55 (0.01 – 1.08)	0.60
Platelets - n x109/L		0.99 (0.98 – 1.01)	0.43
APRI index		4.98 (0.12 - 874.1)	0.42
AST – U/L		1.05 (0.97 – 1.18)	0.29
ALT – U/L		1.08 (1.01 - 1.19)	0.06
γGT – U/L		0.04 (1.00 - 1.11)	0.10
IgG 4 – mg/dL		1.00 (0.99 – 1.00)	0.63
Iron – umol/l		0.98 (0.95 – 1.00)	0.30

Table 3

Predictive factors of liver stiffness in the entire population of IPF patients evaluated for liver stiffness on Fibroscan[®] measurements. Values are expressed as HR (95%CI). Logistic regression analysis in relation to liver stiffness was used to determine the relationship of clinical, functional and serum levels of liver function with liver stiffness development.

		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p Value	HR (95% CI)	<i>p</i> Value
Gender	female	-	-	-	-
	male	1.08 (0.39 – 3.01)	0.87	-	-
Age at diagnosis (<i>years)</i>	< 71	-	-	-	-
	≥ 71	1.46 (0.57 – 3.73)	0.42	-	-
Smoking history (packyears)	< 10	-	-	-	-
	≥10	0.79 (0.25 – 2.46)	0.68	-	-
FVC at diagnosis (%)	≥ 78	-	-	-	-
	< 78	1.40 (0.506 – 3.46)	0.46	-	-
DL _{co} at diagnosis (%)	≥ <i>35</i>	-	-	-	-
	< 35	3.95 (1.46 – 10.7)	0.007	3.18 (0.56 – 17.8)	0.18
GAP score	1	-	-	-	-
	11	1.26 (0.45 – 3.54)	0.66	0.42 (0.07 – 2.49)	0.33
	<i>III</i>	5,40 (1.43 – 20.4)	0.01	3.91 (0.42 – 36.3)	0.22
METAVIR score	FO	-	-	-	-
	F1-F2-F3-F4	2.60 (1.003 - 6.7)	0.04	1.39 (0.50-3.89)	0.51
Platelets - n x109/L	< 250	-	-	-	-
	≥ 250	0.85 (0.30 – 2.42)	0.76	-	-
APRI index	< 0.23	-	-	-	-
	≥ 0.23	2.39 (1.89 – 6.40)	0.01	4.52 (1.30-15.6)	0.02
AST – U/L	< 20	-	-	-	-
	≥ 20	1.54 (0.59 – 3.98)	0.37	-	-
ALT – U/L	< 15	-	-	-	-
	≥15	1.58 (0.62 – 4.04)	0.33	-	-
γGT – U/L	< 21	-	-	-	-
	≥21	2.25 (0.82 – 6.15)	0.11	-	-
Total bilirubin– umol/l	< 0.43	-	-	-	-
	≥0.43	2.16 (0.72 – 6.47)	0.16	-	-
lgG 4 – mg/dL	< 52	-	-	-	-
	≥ 52	0.83 (0.25 – 2.75)	0.76	-	-
Iron – umol/l	< 91	-	-	-	-
	≥91	0.36 (0.10 – 1.34)	0.13	-	-

Ferritin – ug/l	< 99	-	-	-	-
	≥ 99	1.57 (0.14 – 17.7)	0.71	-	-
Transferrin – g/L	< 357	-	-	-	-
	≥ 357	1.46 (0.38 – 5.56)	0.57	-	-

Predictors of overall survival in the population of IPF patients treated with antifibrotics.

Values are expressed as HR (95%CI). Values are expressed as HR (95%CI). Univariate and multivariate Cox proportional hazard regression tests were used to determine the relationship of clinical, functional and serological characteristics with survival.

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03/03/2020

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