Oncomarkers in IPF Patients

Subjects: Pathology

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This paper is a review of the literature on the clinical role of oncomarkers in idiopathic pulmonary fibrosis (IPF) progression, and a description of the routine oncomarker trend in IPF patients over the longest follow-up yet reported. This is the first meta-analysis to review the results of studies evaluating the predictive prognostic value of circulating oncomarkers (CEA, Ca15.3, Ca19.9, Ca125, and KL-6) for IPF. The study focused on the discovery of multiple biomarker signatures, such as combinations of oncomarkers, that are widely and routinely available in biochemistry laboratories.

The combination of clinical parameters and biological markers could help achieve more accurate results regarding prognosis and response to treatment in IPF. Our results could pave the way for a more “personalized” medical approach to patients affected by IPF.

idiopathic pulmonary fibrosis | oncomarker | lung cancer

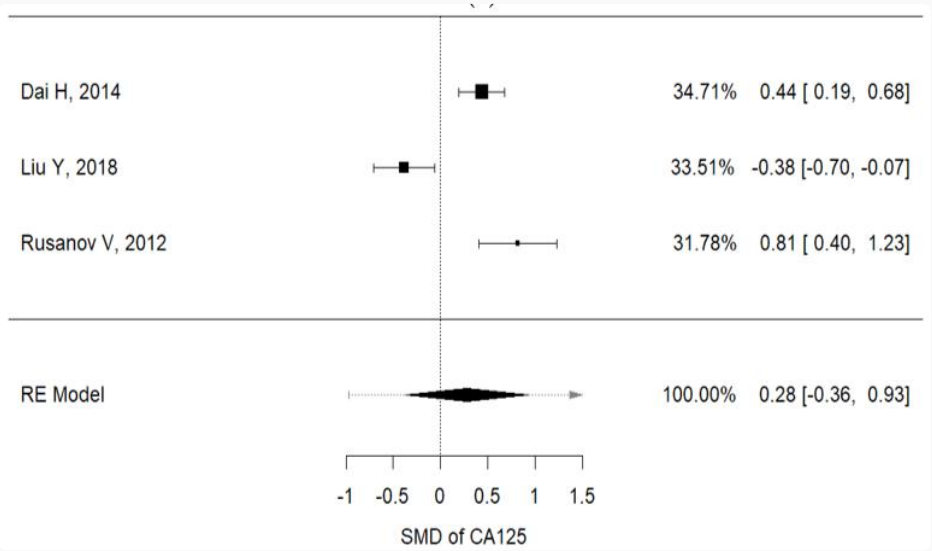
1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs [1]. Recent meta-analyses have shown close associations between the development of IPF and lung cancer [2][3][4]. Both usually affect the periphery of lower lung lobes, sharing common risk factors (e.g., smoking, environmental or occupational exposure, viral infections, and chronic tissue injury) and pathogenic mechanisms, such as epigenetic and genetic alterations, abnormal expression of microRNAs, cell and molecular aberrations (e.g., altered responses to regulatory signals, delayed apoptosis, and reduced cell-to-cell communication), and activation of specific signal transduction pathways [5]. In the PROFILE (prospective observation of fibrosis in the lung clinical endpoints) study, some of these oncomarkers, especially Ca19.9 and Ca125, were associated with increased mortality [6]. Very recently Balestro et al. corroborated the prognostic value of Ca19.9 in end-stage IPF [7]. Although several authors have reported high concentrations of common oncomarkers, including carcinoembryonic antigen (CEA) [8], cancer antigen 19.9 (Ca19.9) [9], 15.3 (Ca15.3) [10], 125 (Ca125) [8], and Krebs von den Lungen-6 (KL-6) [11][12][13][14], in IPF, little data is available on the prognostic role of all these markers, taken together, and their interactions, in IPF progression [9][15].

2. Meta-Analysis Results

Higher concentrations of carcinoembryonic antigen (CEA) and Ca-125 were recorded in IPF patients with lung cancer, than in non-IPF patients (I^2 = 92.3%, p < 0.001, mean CEA concentrations (IPF vs. non-IPF): 5.35 vs. 4.89 ng/mL; I^2 = 91.9%, p < 0.001, mean Ca125 concentrations (IPF vs. non-IPF): 34.68 vs. 32.09 U/mL) (Figure 2a,b).

(**a**)



(**b**)

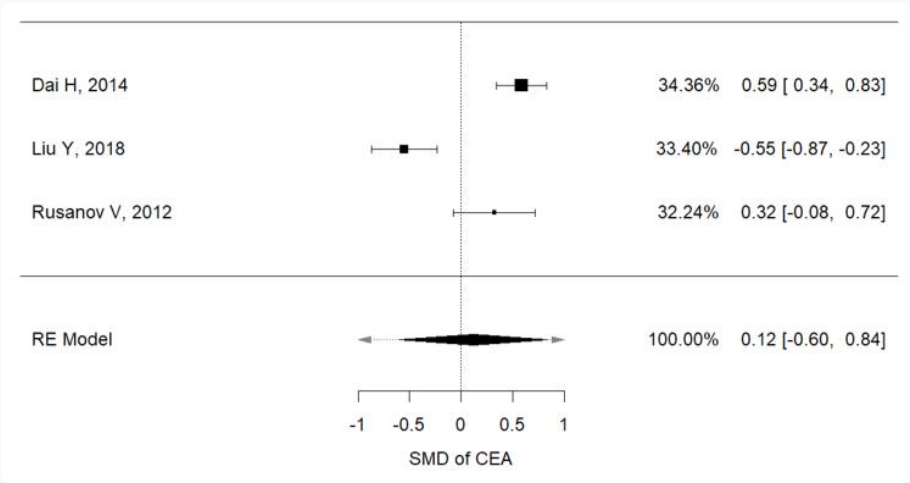
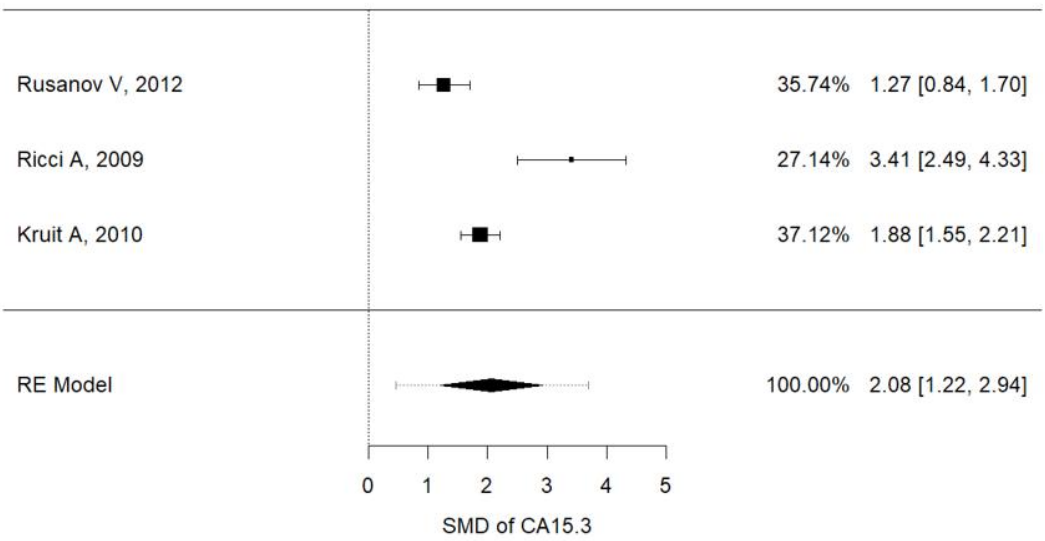
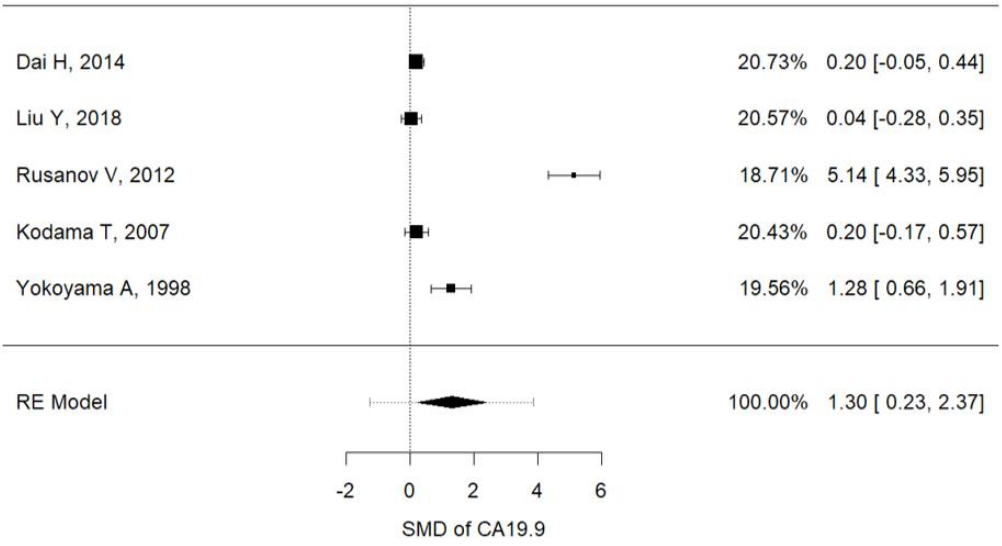


Figure 1. (**a**) Metanalysis results from Ca125 concentrations of selected studies; (**b**) metanalysis results from CEA concentrations of selected studies.

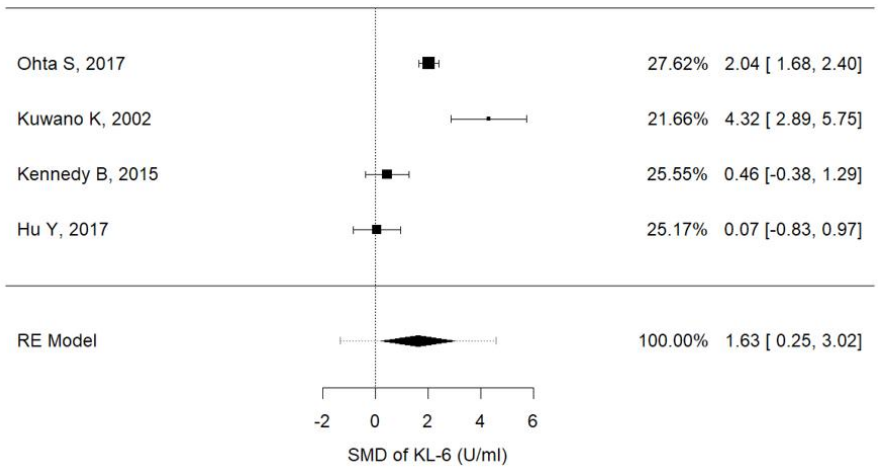
Serum concentrations of Ca15.3 (I^2 = 88.8%, P = 0.001, mean (IPF vs. non-IPF): 91.02 vs. 16.3 U/ml), Ca19-9 (I^2 = 97.3%, $p < 0.001$, mean (IPF vs. non-IPF): 54.71 vs. 15.29 U/ml) and KL-6 (I^2 = 91.9%, $p < 0.001$, mean (IPF vs. non-IPF): 1164 vs. 317 U/ml) were associated with disease progression in IPF patients (Figure 2a–c). In particular, higher values of these three markers were found in IPF patients and were correlated with a worse prognosis.


Rusanov V, 2012
35.74% 1.27 [0.84, 1.70]
Ricci A, 2009
27.14% 3.41 [2.49, 4.33]
Kruit A, 2010
37.12% 1.88 [1.55, 2.21]
RE Model
100.00% 2.08 [1.22, 2.94]
0 1 2 3 4 5
SMD of CA15.3

(**a**)


Dai H, 2014
20.73% 0.20 [-0.05, 0.44]
Liu Y, 2018
20.57% 0.04 [-0.28, 0.35]
Rusanov V, 2012
18.71% 5.14 [4.33, 5.95]
Kodama T, 2007
20.43% 0.20 [-0.17, 0.57]
Yokoyama A, 1998
19.56% 1.28 [0.66, 1.91]
RE Model
100.00% 1.30 [0.23, 2.37]
-2 0 2 4 6
SMD of CA19.9

(**b**)



(**c**)

Figure 2. (**a**) Metanalysis results from Ca15.3 concentrations of selected studies, (**b**) metanalysis results from Ca19.9 concentrations of selected studies, (**c**) metanalysis results from KL-6 concentrations of selected studies.

3. Original Contribution

3.1. Study Population

The main characteristics of our population are reported in Table 1. As expected, IPF patients were predominantly male (81.4%), over 65 years of age and most had a history of cigarette smoking (75%). Velcro crackles were audible by chest auscultation in all IPF patients, and significantly more often than in non-IPF patients (Table 1). Dyspnea expressed as modified Medical Research Council (mMRC) score was statistically different in the IPF and non-IPF groups at t3 (p = 0.0070). In the IPF group, mMRC score at t0 differed from those at subsequent follow-up times (p = 0.0001). At 18-month follow-up (t3), three IPF patients had died, while no patient had died in the non-IPF group. Stratifying the study population according to therapy with pirfenidone or nintedanib, we did not observe any statistically significant difference of oncomarker concentrations or functional disease progression.

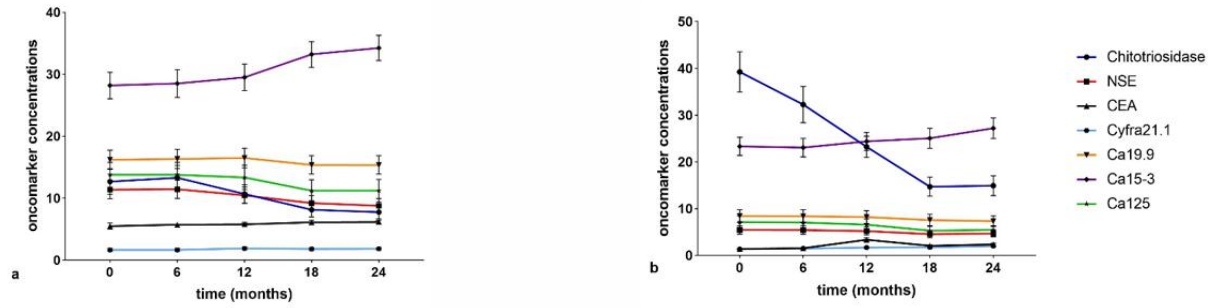
Table 1. The main characteristics of our population divided in idiopathic pulmonary fibrosis (IPF) and non-IPF groups. 1 and 2: older and prevalence of males in the IPF group (p < 0.05), respectively. 3. Velcro sound was prevalent in the IPF group (p < 0.05). Abbreviations: modified Medical Research Council (mMRC).

	IPF (n = 24)	Non-IPF (n = 25)
Age (yr)	73.80 ± 7.79 [1]	62.43 ± 13.63

Sex (M/F)	22/2 [2]	14/11
Smoking history (>5p/yr)	18/24	12/25
Familiarity for ILD (yes/no)	2/24	1/25
Cough (VAS > 3/10 cm)	22/24	17/25
Dyspnea (mMRC > 1/4)	16/24	14/25
Velcro sound (yes/no)	23/24 [3]	8/25
Clubbing (yes/no)	3/24	1/25

Statistical analysis was performed comparing each sampling time for each group (IPF: t0 vs. t1, t0, vs. t2, etc.); moreover, a comparison analysis was performed between the two subgroups (IPF t0 vs. non-IPF t0, IPF t1 vs. non-IPF t1, etc.).

Serum concentrations (Figure 3a,b) of chitotriosidase and oncomarkers Cyfra 21.1, Ca19.9, and Ca125 were in the normal range at t0 in the IPF and non-IPF groups. As expected, serum chitotriosidase was higher in the non-IPF group in relation to the presence of sarcoidosis patients ($p < 0.05$) [16][17][18][19][20]. This trend remained unchanged even at 18-month follow-up.



(**a**) (**b**)

Figure 3. (**a**) Serial concentrations of oncomarkers in the IPF group. (**b**) Serial oncomarker concentrations in the non-IPF group.

The non-IPF group showed lower CEA concentrations at t0 than at t3 (p = 0.0294) and t4 (p = 0.0019) and the difference was statistically significant between t1 and t4 (p = 0.0327). Comparing oncomarker concentrations in the two groups, neuron specific enolase (NSE), CEA, Ca19.9 and Ca125 were higher in IPF patients than in the non-IPF group at every follow-up ($p < 0.05$). Ca15.3 concentrations were higher in the IPF than the non-IPF group at t3 (p = 0.0080) and t4 (p = 0.0168).

In IPF group patients, serum concentrations of Ca15.3 showed a statistically significant increase in the intervals t0–t3 (p = 0.0369), t0–t4 (p = 0.0142), t1–t3 (p = 0.0350), and t2–t4 (p = 0.043).

CEA had the greatest sensitivity and specificity for distinguishing IPF and non-IPF patients at all follow-up times (Table 2).

Table 2. Receiver operating characteristic (ROC) curve analysis between IPF and non-IPF patients according to oncomarker concentrations at each sampling time. Abbreviations: t0, baseline; t1, 6 months; t2, 12 months; t3, 18 months; t4, 24 months.

IPF vs. Non-IPF	AUC	*p* Value	Cut-Off Value	Sensitivity	Specificity
NSE, T0	76	0.0016	7.75	72	70.8
NSE, T1	77.1	0.0012	4.96	68	79.2
NSE, T2	76.7	0.0014	7.95	72	66.7
NSE, T3	77.4	0.0010	4.65	72	75
NSE, T4	71.6	0.0096	5	72	70.8
CEA, T0	94	<0.0001	2.55	96	87.5
CEA, T1	99.7	<0.0001	2.85	96	95.8

CEA, T2	95.6	<0.0001	2.85	92	95.5
CEA, T3	98.8	<0.0001	2.85	88	95.8
CEA, T4	98.1	<0.0001	3.3	88	95.8
Ca19.9, T0	78.4	0.0006	12.6	76	79.2
Ca19.9, T1	77	0.0012	11.9	72	79.2
Ca19.9, T2	78.2	0.0007	11.2	68	79.2
Ca19.9, T3	79.6	0.0004	9.7	68	79.2
Ca19.9, T4	81.6	0.0002	8.3	68	83.3
Ca15-3, T3	69.9	0.0168	31.6	72	54.2
Ca15-3, T4	67.7	0.0340	29.3	60	62.5
Ca125, T0	71.4	0.0114	8.8	68	66.7
Ca125, T1	72.1	0.0008	8.7	68	66.7
Ca125, T2	74.2	0.0036	9.3	68	66.7
Ca125, T3	73.8	0.0042	7.2	72	66.7
Ca125, T4	71.5	0.0099	9.5	76	62.5

In order to improve the specificity and sensitivity of Ca15.3, a panel of biomarkers was analyzed. With the IPF group as dependent variable, and chitotriosidase, Cyfra 21.1, Ca15.3, Ca125, and Ca19.9 concentrations at t0 as independent variables, the area under the receiver operating curve (AUROC) obtained by logistic regression was 88% (95% CI 78–97, NPP 82.6%, and PPP 76.9%, $p < 0.0001$) (Figure 4). With the same biomarker concentrations at t1, t2, t3, and t4 as independent variables, we repeated the logistic regression. At t1, we obtained an AUROC of 85% (95% CI 74–95, NPP 70.8%, and PPP 68%, $p < 0.0001$) (Figure 4), at t2, 86% (95% CI 76–96, NPP 78.3%, and PPP 73.1%, $p < 0.0001$) (Figure 4), at t3, 86% (95% CI 76–96, NPP 80%, and PPP 79.2%, $p < 0.0001$) (Figure 4) and at t4, 86% (95% CI 75–96, NPP 78.3%, and PPP 73.1%, $p < 0.0001$) (Figure 4). With respect to a single biomarker, the panel increased sensitivity and specificity in discriminating the two groups at all follow-up times.

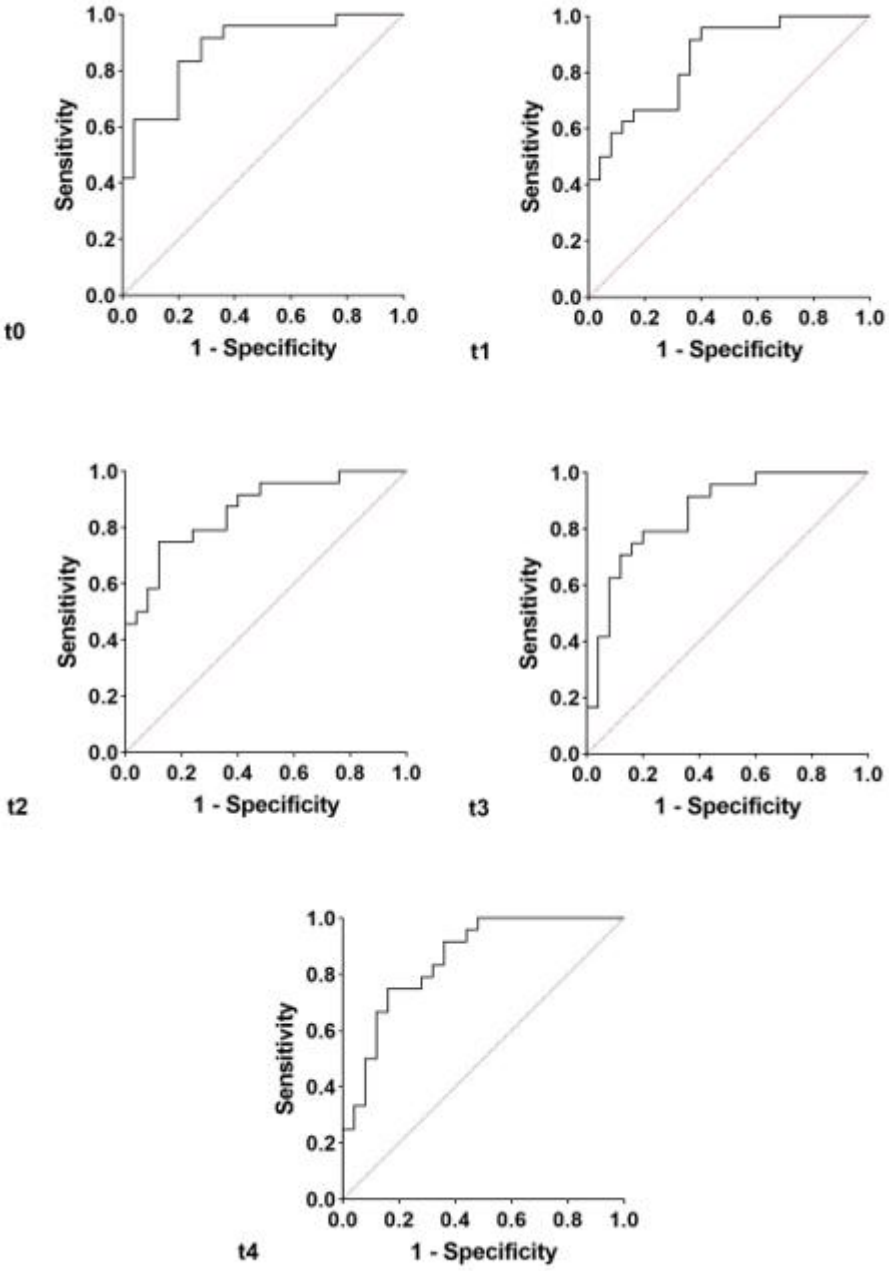


Figure 4. The analysis of logistic regression reporting t0, t1, t2, t3, and t4 oncomarkers panel in the IPF vs. the non-IPF group.

Regarding lung function (Figure 5), FVC%, forced expiratory volume in 1 sec (FEV1%), total lung capacity (TLC)%, and DLCO% decreased significantly in the interval t0–t4 in IPF patients compared to non IPF patients. TLC and DLCO percentages were lower in the IPF than in the non IPF group at all follow-ups. In IPF patients, all functional parameters were significantly different ($p < 0.01$) at t3 with respect to t2 and t0 ($p < 0.01$). No significant differences ($p > 0.01$) in lung function parameters were observed in non-IPF patients in the serial follow-up.

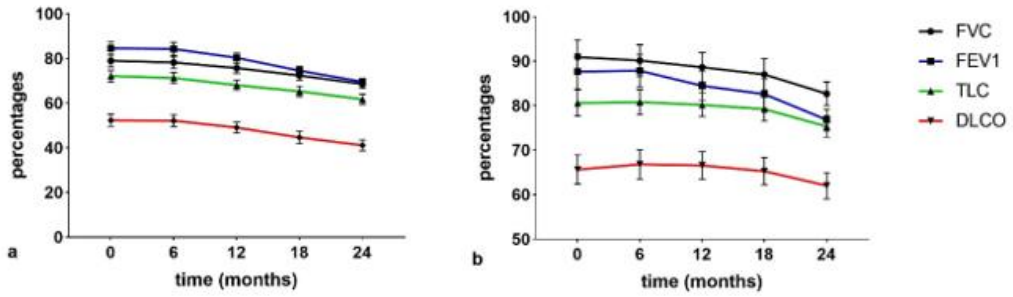


Figure 5. (**a**) IPF serial changes of pulmonary function test (PFT) parameters (**b**) non-IPF serial changes PFT parameters.

The trend of functional parameters in the IPF population showed a progressive statistically significant decline at t3 and t4 ($p < 0.05$). Due to the limited statistical sample, no correlations between serological biomarkers and survival data could be detected. Correlation analysis between serum biomarkers and lung function parameters in the two groups are shown in Table 3. Interestingly, there was a significant negative correlation between serum concentrations of CEA and FEV1, FVC and DLCO percentages at t3 and t4.

Table 3. Correlation analysis between serum biomarkers and pulmonary function test (PFT) parameters in the two subgroups. Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusing lung for carbon monoxide; CEA, carcinoembryonic antigen; TLC, total ling capacity.

IPF		Rho Coefficient	*p* Value	Non-IPF		Rho Coefficient	*p* Value
T0				T0			
CEA	TLC	−0.48	0.018	Chito	FVC	0.476	0.016
Cyfra21.1	DLCO	−0.43	0.036		FEV1	0.425	0.034

T1					TLC	0.422	0.035
Chito	DLCO	0.511	0.011	T1			
Cyfra21.1	DLCO	−0.44	0.031	Chito	FVC	0.605	0.001
T2					FEV1	0.662	0.0003
CEA	FVC	−0.501	0.013		TLC	0.515	0.008
CEA	FEV1	−0.524	0.009		DLCO	0.490	0.013
Cyfra21.1	FEV1	−0.430	0.036	T2			
T3				Chito	FVC	0.636	0.0006
Chito	FVC	0.416	0.043		FEV1	0.710	0.0001
Chito	FEV1	0.429	0.037		TLC	0.522	0.0075
CEA	FVC	−0.682	0.0002		DLCO	0.477	0.0252
CEA	FEV1	−0.811	0.000001	NSE	TLC	−0.480	0.015
CEA	DLCO	−0.647	0.001	CEA	FEV1	−0.529	0.007
Ca19.9	FVC	−0.458	0.024		TLC	−0.418	0.038
Ca15-3	FEV1	−0.439	0.032		DLCO	−0.423	0.035

T4				Ca19.9	TLC	−0.411	0.041
Chito	FEV1	0.54	0.006	T3			
CEA	FVC	−0.803	0.000002	Chito	FVC	0.635	0.0006
CEA	FEV1	−0.852	0.0000001		FEV1	0.783	0.000004
CEA	TLC	−0.464	0.022		TLC	0.579	0.002
CEA	DLCO	−0.520	0.009		DLCO	0.509	0.0093
Cyfra21.1	FVC	−0.427	0.037	NSE	TLC	−0.510	0.009
	FEV1	−0.505	0.012		DLCO	−0.410	0.0417
				CEA	TLC	−0.461	0.02
				Ca19.9	TLC	−0.461	0.0387
				Ca125	TLC	−0.408	0.0431
				T4			
				Chito	FVC	0.614	0.001
					FEV1	0.711	0.00007
					TLC	0.598	0.002

		DLCO	0.485	0.014
	NSE	TLC	−0.431	0.032
	Ca19.9	TLC	−0.419	0.037
	Ca125	TLC	−0.405	0.045

Abbreviations: t0, baseline; t1, 6 months; t2, 12 months; t3, 18 months; t4, 24 months.

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