

Clinical Characteristics and Survival According to the Presence of Velcro Crackles in the European MultiPartner IPF Registry (EMPIRE)

Rationale:

Patients with idiopathic pulmonary fibrosis (IPF) frequently present with inspiratory “velcro” crackles (VC) in auscultation. These are associated with features of the usual interstitial pneumonia pattern in high-resolution computed tomography (HRCT) and have been suggested as a tool for screening and early diagnosis of IPF. We aimed to assess the prevalence of VC and its association with clinical features and prognosis in the prospective European MultiPartner IPF Registry (EMPIRE).

Methods:

In EMPIRE, demographics and clinical data like medical history, HRCT features and pulmonary function tests (PFT) were collected at baseline and every six months during follow up. The presence of VC was determined only upon inclusion into the registry. Analyses were performed separately for patients with prevalent IPF at enrollment and incident IPF, when diagnosed within 6 months before inclusion. Baseline characteristics in different subgroups were compared using Pearson's Chi-squared test, the Wilcoxon rank sum test or Fisher's exact test according to normal distribution and scales of measurement. Overall survival (OS) was analyzed by Kaplan–Meier estimates, log-rank test, and Cox proportional hazards models. OS was both calculated from reported diagnosis of IPF as well as from registry enrollment.

Results:

In a total of 4583 IPF patients (71% men, median age 70 (interquartile range 64–75)), 4077 (89%) were reported positive for VC at registry enrollment, while 506 (11%) were not. Similarly, in 3347 incident IPF cases, VC were present in 2942 (88%) patients and absent in 405 (12%). As shown in table 1, incident patients without VC were significantly younger, had a shorter duration of symptoms, less comorbidities and comedications and less frequently presented with a definite UIP pattern. Also, their PFT showed less impairment, and a significantly higher fraction of patients without VC had lower GAP and NYHA stages as compared to patients with VC. In the 1236 patients enrolled with prevalent IPF, these findings were generally similar, but less pronounced.

Overall survival in incident patients from registry enrollment did not significantly differ between patients with VC as compared to those without (hazard ratio (HR) 1.13 (95% confidence interval (CI) 0.92–1.38), p=0.23). Similarly, there was no significant survival difference, when OS was calculated in all patients from reported IPF diagnosis on (HR 0.99 (95% CI 0.83–1.18), p=0.92).

Conclusions:

Patients who did not have VC upon inclusion into EMPIRE had less advanced disease, but no significantly different overall survival. This challenges the potential role of auscultation as a screening tool for early IPF.

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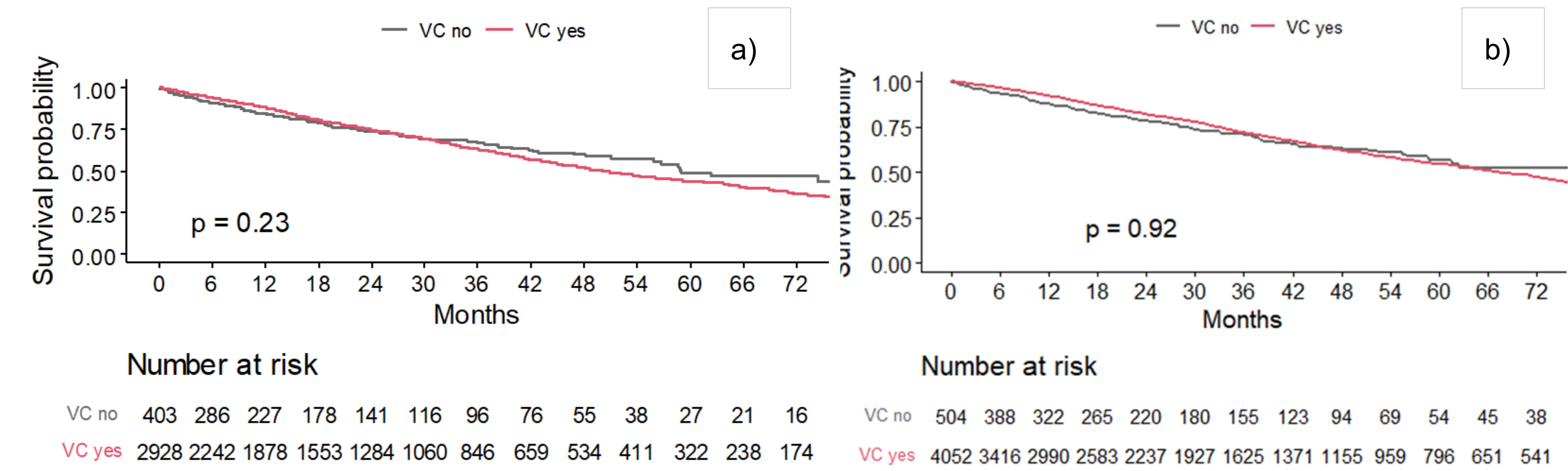


Figure 1. Overall survival of incident patients with and without velcro crackles from registry enrollment on (a) and in all patients from reported IPF diagnosis on (b).

Table 1. Baseline characteristics of patients with and without velcro crackles - by incident and prevalent IPF cohorts

Characteristic	Incident cases			Prevalent cases		
	VC no, N=405	VC yes, N=2,942	p-value ²	VC no, N=101	VC yes, N=1,135	p-value ²
Men, n (%)	304 (75.1)	2,119 (72.0)		69 (68.3)	779 (68.6)	0.947
Age at baseline (years)			0.014			0.051
N	405	2,942		101	1,135	
Mean (SD)	68 (11)	70 (9)		67 (9)	69 (9)	
Median (25%–75%)	69 (63–75)	70 (65–76)		67 (62–73)	69 (63–75)	
Duration of symptoms (months)			<0.001			0.040
N	340	2,834		89	1,020	
Mean (SD)	13 (22)	19 (28)		14 (23)	19 (29)	
Median (25%–75%)	6 (2–12)	12 (6–24)		6 (3–12)	11 (5–24)	
Smoking status, n (%)			0.008			0.687
Never-smokers	146 (37.2)	1,140 (39.8)		35 (35.4)	436 (39.4)	
Light smokers (<20 py)	61 (15.5)	584 (20.4)		20 (20.2)	196 (17.7)	
Moderate/heavy smokers (≥20+ py)	186 (47.3)	1,140 (39.8)		44 (44.4)	474 (42.9)	
HRCT pattern, n (%)			<0.001			<0.001
UIP	226 (55.8)	1,946 (66.1)		54 (53.5)	814 (71.7)	
Probable, possible UIP	151 (37.3)	816 (27.7)		38 (37.6)	233 (20.5)	
Inconsistent with UIP	15 (3.7)	92 (3.1)		7 (6.9)	64 (5.6)	
Unknown	13 (3.2)	88 (3.0)		2 (2.0)	24 (2.1)	
Number of comorbidities			0.006			0.962
N	405	2,942		101	1,135	
Mean (SD)	3.52 (2.20)	3.92 (2.54)		4.10 (2.48)	4.24 (2.79)	
Median (25%–75%)	3.00 (2.00–5.00)	4.00 (2.00–5.00)		4.00 (3.00–6.00)	4.00 (2.00–6.00)	
Number of comedications			<0.001			0.518
N	364	2,548		85	968	
Mean (SD)	2.88 (1.62)	3.37 (1.93)		3.39 (1.77)	3.31 (1.91)	
Median (25%–75%)	3.00 (2.00–4.00)	3.00 (2.00–5.00)		3.00 (2.00–4.00)	3.00 (2.00–5.00)	
Antifibrotics, n (%)	272 (67.2)	2,052 (69.7)	0.289	41 (40.6)	729 (64.2)	<0.001
Rehabilitation, n (%)	28 (6.9)	687 (23.4)	<0.001	11 (10.9)	175 (15.4)	0.223
LTOT, n (%)	53 (13.1)	727 (24.7)	<0.001	19 (18.8)	432 (38.1)	<0.001
FVC predicted (%)			<0.001			0.033
N	350	2,618		87	976	
Mean (SD)	83 (22)	79 (20)		82 (26)	76 (23)	
Median (25%–75%)	83 (68–97)	78 (65–91)		83 (63–100)	74 (59–92)	
DLCO predicted (%)			<0.001			<0.001
N	305	2,369		73	809	
Mean (SD)	55 (22)	49 (17)		57 (24)	47 (18)	
Median (25%–75%)	53 (39–67)	47 (37–59)		54 (43–72)	45 (33–58)	
6MWD (m)			0.755			0.707
N	264	1,265		54	525	
Mean (SD)	377 (118)	379 (118)		394 (114)	381 (117)	
Median (25%–75%)	387 (305–462)	390 (314–457)		402 (303–472)	395 (320–458)	
GAP index, n (%)			0.003			0.108
GAP I	184 (55.1)	1,136 (45.4)		42 (52.5)	384 (43.2)	
GAP II	127 (38.0)	1,126 (45.0)		33 (41.2)	386 (43.4)	
GAP III	23 (6.9)	238 (9.5)		5 (6.2)	119 (13.4)	
Dyspnoea (NYHA grade), n (%)			<0.001			0.437
I	86 (24.8)	143 (5.2)		6 (6.9)	45 (4.4)	
II	160 (46.1)	1,644 (59.5)		52 (59.8)	595 (57.9)	
III	100 (28.8)	938 (33.9)		29 (33.3)	367 (35.7)	
IV	1 (0.3)	39 (1.4)		0 (0.0)	20 (1.9)	

²Pearson's Chi-squared test; Wilcoxon rank sum test, Fisher's exact test

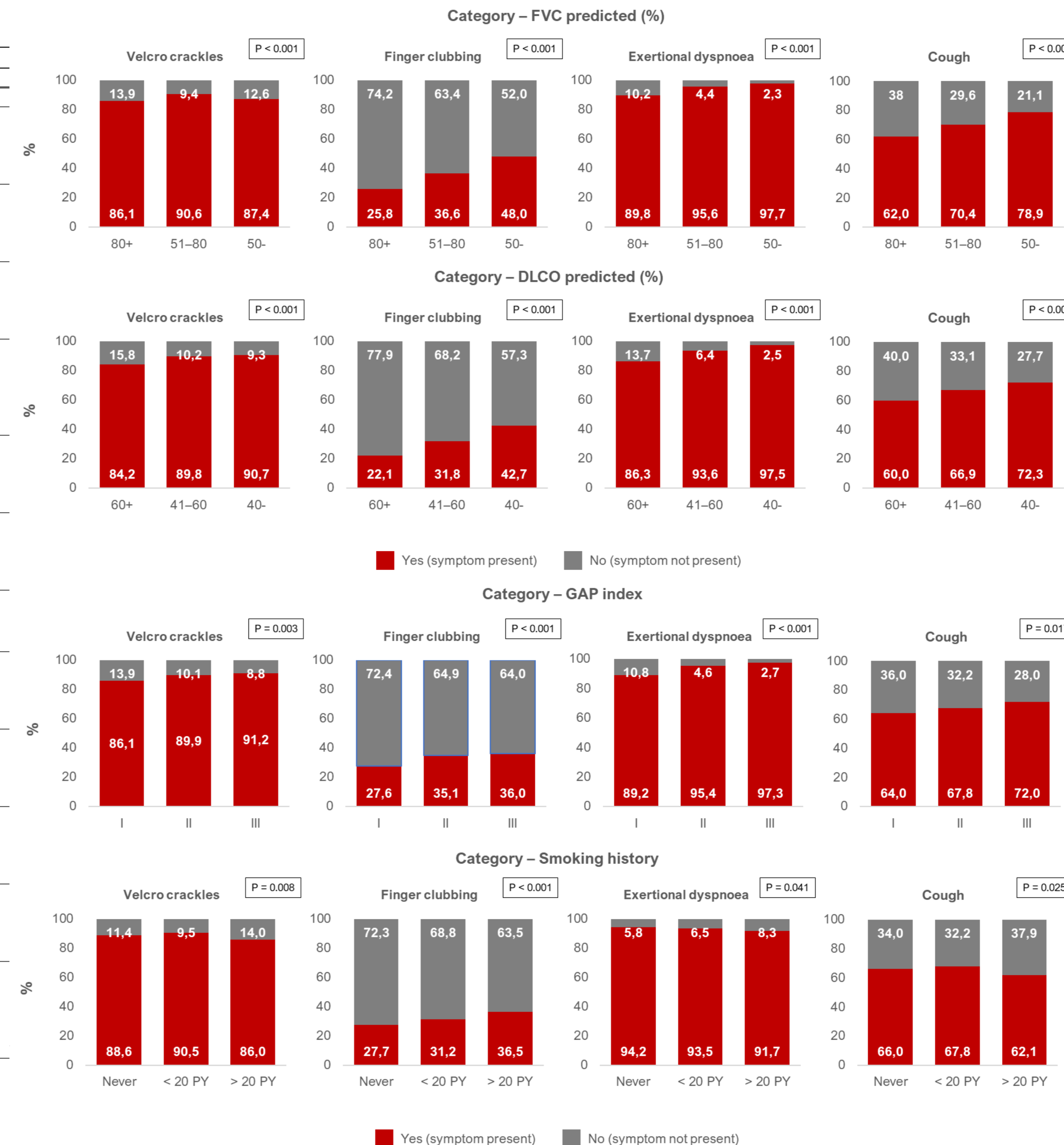


Figure 2. Frequency of IPF signs and symptoms according to categories of FVC and DLCO



Figure 3. Frequency of IPF signs and symptoms according to GAP score and categories of cigarette smoking pack years

