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RESEARCH

IDIOPATHIC PULMONARY FIBROSIS

Use of Telomere Length as a Biomarker in Idiopathic Pulmonary Fibrosis

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Abstract

Background Telomere shortening, a hallmark of cellular aging, is associated with poor outcomes in idiopathic pulmonary fibrosis (IPF). This study aimed to explore the relationships between telomere length (TL), pulmonary function tests, and telomere-related gene (TRG) mutations in a real-world IPF population.

Methods We included IPF patients from two Belgian academic hospitals, collecting demographic and clinical data. TL was measured using Flow-FISH and expressed as a percentile. Short TL was defined as below the 10th percentile (P10), and very short TL as below the 1st percentile (P1).

Results We analysed 143 patients (106 men, 74%), with a median age of 70 years. Thirty patients (21%) met the European Respiratory Society (ERS) criteria for familial pulmonary fibrosis (FPF). Short TL was found in 74 patients (50%), predominantly in men ($p<0.05$). Patients with short TL experienced a greater decline in lung function over 24 months compared to those with normal TL (− 4% vs + 3% FVC, $p<0.05$; − 7% vs − 3% DLCO, $p<0.05$). Patients with very short TL were younger at diagnosis and tended to have a more pronounced FVC decline (− 5% vs − 1%, $p=0.06$). TRG variants were identified in 16 individuals, occurring more frequently in those with short (14/27, 52%) or very short TL (10/20, 50%).

Conclusion Short TL is common in both sporadic and familial IPF and serves as a predictive biomarker for accelerated lung function decline. Additionally, the presence of short TL is indicative of an underlying TRG mutation.

Keywords Pulmonary fibrosis · Telomeres · Biomarker

Caroline Dahlqvist and Thomas Planté-Bordeneuve contributed equally to the work.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and severe lung disease characterized by excessive extracellular matrix deposition resulting in respiratory insufficiency and death. While the exact sequence of events leading to IPF remains to be fully determined, telomere shortening and early senescence are involved [1]. Several pathogenic variants in telomere related genes (TRG) are associated with telomere shortening and short telomere syndrome (STS) [2]. Telomeres are repetitive nucleotides sequence located at the extremities of chromosomes that protect genomic integrity [3]. The maintenance of telomere length (TL) is principally regulated by telomerase and shelterin complexes [4, 5]. Defects in telomere maintenance mechanisms result in premature telomere shortening leading to cellular apoptosis and senescence, two key processes in pulmonary fibrosis [6]). Pathogenic genetic variants impacting telomere

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maintenance processes have been identified as a risk factor for developing IPF and are present in 5–10% of IPF patients [7]. Besides the aforementioned germline variants, aging and some environmental factors such as smoking also contribute to TL shortening [8], explaining why even in the absence of a TRG pathogenic variant, IPF patients may display short telomeres [9]. Additionally, short TL results in poorer outcome in this disease [10–14]. While the link with IPF has been extensively described in dedicated studies, the exact real-world clinical impact is less documented. Furthermore, while very short telomere length (below the 1st percentile) exposes patients to extrathoracic manifestations of STS [11], whether it modifies the course of pulmonary fibrosis remains unknown. TL can directly be measured in circulating peripheral white blood cells, lymphocytes and granulocytes in particular, by various techniques of which Flow-FISH is currently considered the most reproducible [2, 11]. In the present study, we aimed to study the impact of telomere length on outcome and on the decision to propose genetic screening. We specifically compared individuals with normal, short (< P10) and very short (< P1) TL.

Methods

Population and Study Measures

All patients from two Belgian tertiary hospitals (Cliniques universitaires Saint Luc, Brussels and CHU-UCL Namur, Yvoir) with a diagnosis of IPF, based on the 2018 American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [15] made between September 2016 and January 2023 were eligible for inclusion in this observational cohort study. The diagnosis was obtained through multidisciplinary discussions (MDD) based on clinical, radiological, and when indicated, histological data. Clinical data were collected from the electronic medical record (EMR), including age at diagnosis sex, smoking habits, familial history of interstitial lung disease and TL measurement. All high-resolution CT scans (HRCT) were centrally reviewed during MDD. Lung function tests were recorded at diagnosis and then at 6-, 12- and 24-months post-diagnosis. Familial occurrence of fibrosis was systematically queried during routine consultations for all patients. Familial pulmonary fibrosis (FPF) occurrence was defined as per recent ERS guidelines [2]. GAP index at diagnosis was calculated for each patient [16].

Telomere Length Measurements and Exome Sequencing

Telomere length was measured by flow-FISH in all patients and plotted against TL of a published non-IPF control database of all ages (0–99 years) as previously described [17], (Figure S1). Briefly, following red blood cell lysis with ammonium chloride, white blood cells were frozen at − 80 °C until analysis. Aliquots of calf thymus were mixed to each sample for internal control. Telomeres were stained with FITC-labelled $(CCCTAA)_3$ PNA probe (Panagene, Digeon, South Korea) and fluorescence was measured with a Navios EX flow cytometer (Beckman Coulter, Pasadena, CA, USA). Patients with TL above or equal to 10th percentile (P10) were considered to have normal TL. Short TL was defined as a TL below the 10th percentile for age, and very short TL below or equal to the 1st percentile (P1). Genetic testing was proposed to patients fulfilling FPF criteria according to the recent ERS statement [2] and to patients with short telomere length with a relevant clinical history. Of note, final decision to test was left to physician's discretion. Informed consent was mandatory, according to the Belgian national regulations. Genetic analysis was performed by whole exome sequencing and evaluated for variants of interest in telomere related genes. Genetic testing was left to investigator's discretion and following specific informed consent from the patient. Variants were classified based on the American College of Medical Genetics and Genomics 2015 criteria [18].

Statistics

The study population was separated into patients with normal, short (< P10) and very short (< P1) TL. Between group comparisons were compared by Mann Whitney U test for continuous variables and χ^2 or Fisher exact test for categorical variables when appropriate. Survival analysis was performed using a Kaplan–Meier approach and Log-rank test (final date of analysis 31-12-2023). All data are presented as median and interquartile range. A p-value < 0.05 was considered significant.

Ethical Considerations

All patients provided informed consent prior to inclusion. Patients who underwent genetic testing provided a separated signed informed consent, in accordance with the Belgian law. This study was approved by the local ethical committees (PNEU-ILD-01, 2017/JAN/210, PNEU-ILD-04, 2021/06AOU/336 and 28.2025).

Results

Baseline Characteristics

Baseline characteristics at diagnosis of the 143 included patients are listed in Table 1. Most patients were males

Table 1 Clinical characteristics of the total population subanalysis in function of telomere length

	Total population n = 143	TL < p10 n = 74	TL ≥ p10 n = 69	TL < p1 n = 42	TL > p1 n = 101
Age at diagnosis, years (median (IQR))	70 (64–75)	70 (64–74)	70 (64–76)	67 (63–72)*	71 (65–76)*
Sex, male (n (%))	106 (74)	61 (82) *	45 (65%) *	33 (79)	73 (73)
Smoking status, ever/never (n(%))	104 (73)/39 (27)	53 (72)/21 (28)	51 (74)/18 (26)	32 (76)/10 (24)	72 (71)/29 (29)
Pack years, number (n(%))	25 (10–40)	20 (10–40)	25 (10–40)	18 (10–39)	25 (12–40)
UIP pattern on HRCT, UIP, pUIP, indUIP, alt (n)	41)/49/46/7	24)/23/23/4	17/26/23/3	14/10/15/3	27/39/31/4
Lung biopsy performed (n(%))	61 (43)	28 (38)	33 (48%)	19 (45%)	42 (42%)
TRG variant screening (n(%))	37 (26)	27 (36)*	10 (14%)*	20 (48%)*	17 (17%)*
Identification of TRG variant (n(%))	16 (11)	14 (19) *	2 (3%) *	10 (24%)*	6 (6%)*
Baseline FVC, %PV (median (IQR))	85 (72–97)	83 (71–96)	85 (73–99)	84 (73–95)	85 (72–98)
Baseline DLCO %PV (median (IQR))[#]	57 (44–72)	57 (44–72)	58 (44–72)	57 (46–73)	57 (44–71)
Baseline GAP score (median (IQR))	3 (2–4)	3 (3–4)	3 (2–4)	3 (2–4)	3 (2–4)

Total population (white column) and population analysis based on telomere length below the 10th (light grey) and 1st percentile (dark grey) compared to individuals respectively above these thresholds. All continuous data are expressed as median and interquartile range. A Mann Whitney U test was used for between group comparison of continuous variables. χ^2 or when appropriate Fisher exact test were used for intergroup comparison of categorical variables. * $p < 0.05$. TL: telomere length, p10: percentile 10, p1: percentile 1, IQR: interquartile range, UIP: usual interstitial pneumonia, HRCT: high resolution CT, pUIP: probable UIP, indUIP: indeterminate for UIP, alt: alternative pattern, TRG: telomere related genes, FVC: forced vital capacity, DLCO, diffusion capacity of the lung for carbon monoxide, PV: predicted values. #: missing data n = 2

(74%), 73% of patients were former smokers (median 25 pack-year units) and 92% received antifibrotics (39% pirfenidone, 40% nintedanib, 13% received both sequentially). Median forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) at baseline were 85% and 57% respectively. Radiological pattern evaluation of baseline HRCT revealed a UIP or probable UIP pattern in 90 (63%) while 61 (43%) patients underwent lung biopsy, with 60 (98% of biopsies) showing a histological UIP or probable UIP pattern. One patient had an "indeterminate for UIP" histological pattern, leading to a working diagnosis of IPF assessed in MDD. At the time of diagnosis 90 patients had a GAP index between 0 and 3 (GAP I), 49 between 4–5 (GAP II) and 4 between 6 and 8 (GAP III).

Seventy-four (52%) patients had short TL (< P10) including 42 (29%) with very short (< P1) TL (Fig. 1A, B). No difference in age at diagnosis could be found in individuals with short telomeres compared to patients with normal TL (70 *vs* 70 years, p = 0.41) but patients with very short TL were significantly younger than those above P1 (67 *vs* 71 years, p = 0.03). There was a higher proportion of men in the group with short TL compared to other patients (82 *vs* 65%, p = 0.02) but not in the group with very short TL (p = 0.53). There was no significant difference in smoking status and numbers of pack years between patients with normal TL and patients with short or very short TL. Additionally, the proportion of patients with a UIP or probable UIP pattern on the HRCT was similar, regardless of TL (64% *vs* 62% for short TL *vs* normal TL, p = 1.00 and 57% *vs* 65% for TL < P1 *vs* TL > P1, p = 0.44). Baseline FVC or DLCO did not differ between groups (Table 1).

Thirty patients (21%) fulfilled the ERS criteria for FPF. These patients were significantly younger than sporadic IPF patients (63 vs 71 years, p < 0.001) and tended to present more frequently with short telomeres (67% vs 48%, p = 0.099). In addition, a strong tendency towards a less frequent positive smoking history (57% vs 74%, p = 0.072) was observed while the number of pack-years was similar (20 vs 24, p = 0.466). No significant differences could be found in baseline FVC or DLCO measures (82 vs 85%, p = 0.55 and 62 vs 57%, p = 0.44 respectively) nor in HRCT pattern (UIP or probable UIP present in 53 vs 65%, p = 0.28) with the sporadic population.

Genetic Evaluation

Thirty-seven (26%) patients were evaluated for the presence of TRG variants. Patients with short telomeres were more likely to be evaluated than patients with normal TL (27/74 (36%) vs 10/69 (14%) OR: 3.4 (1.5–7.6), p = 0.003) as were patients with very short TL (20/42 (47%) vs 17/101 (16%), OR 4.5 (2.0–9.8), p < 0.001). Patients screened for TRG variants were also significantly younger than other patients (63 (55–67) vs 71 (67–76) years, p < 0.001) and more likely to fulfil FPF criteria (25/37 (68%) screened vs 5/112 (4.7%) for unscreened, OR: 43.0 (13.8–112.9), p < 0.001). Additionally, we found more variants in patients with short TL (14/27 (52%) vs 2/10 (20%), p = 0.13) and very short TL (10/20 (50%) vs 6/17 (35%) p = 0.51). A total of 17 variants

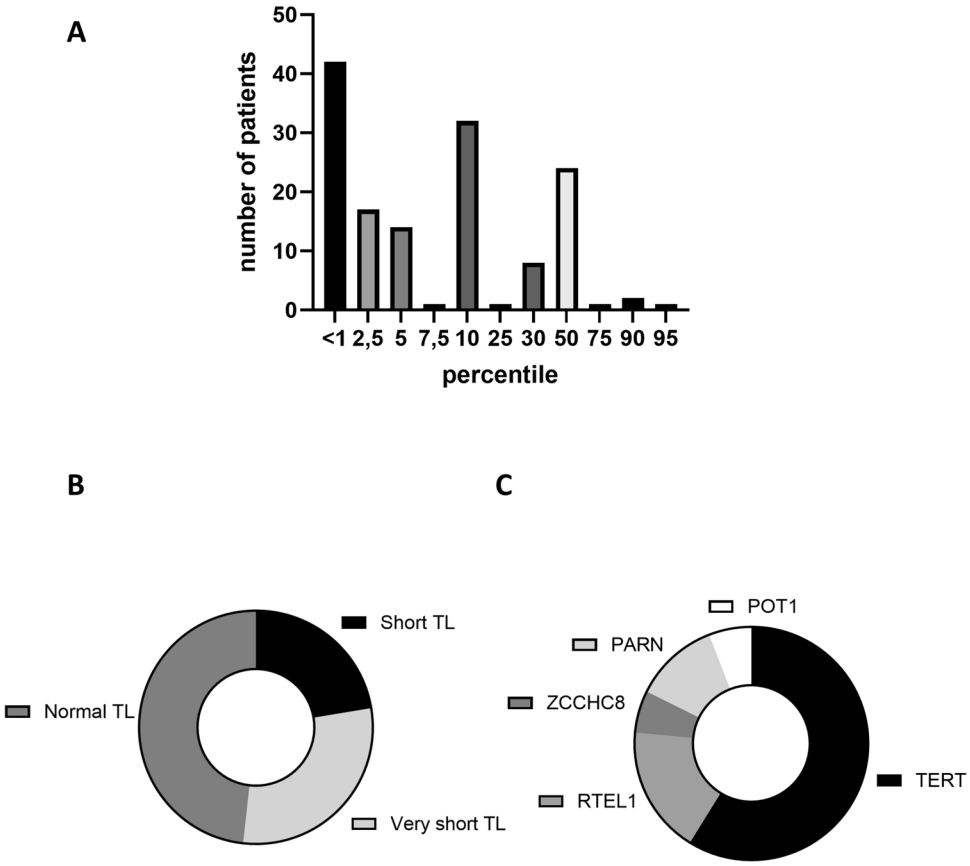

Fig. 1 Distribution of telomere length and variants in telomere related genes. **A, B** Distribution of TL percentiles among the cohort **C.** Frequency of variants in telomere related genes

in TRG were found in 16 individuals (*TERT* n = 9, *RTEL1* n = 3, *ZCCHC8* n = 1, *PARN* n = 3, *POT1* n = 1, Fig. 1C), with 7 variants classified as being of unknown significance (VUS), 5 as likely pathogenic and 5 as pathogenic. Of note, one patient presented with a VUS in *PARN* (c.145A > G) and a likely pathogenic variant in *TERT* (c.2379G > T). All likely pathogenic and pathogenic variants were found in the short telomere group. Very short TL patients were comparatively tested more frequently than individuals between P1-P10 (48 vs 22%, p = 0.029). Class 3–5 variants were found in similar proportions in sporadic and familial patients (42 vs 44%, p = 0.99).

Notably, FPF patients with a TRG variant had a lower baseline FVC (71 vs 86%, p = 0.01) and DLCO (47 vs 71%, p = 0.002) than familial patients without an identified variant.

Comparison of Short and Very Short Telomere Patients

Patients with very short telomeres were significantly younger than patients with TL between P10 and P1 (67 vs 71 years, p = 0.046). They did not differ regarding sex (male/female 33/9 vs 28/4, p = 0.370), smoking habits, number of pack-years, HRCT pattern (UIP or probable UIP 24/42 (57%) vs 23/32 (72%), p = 0.229), baseline FVC (84 vs 81%, p = 0.495), DLCO (57 vs 51%, p = 0.379) or frequency of identified variant (10/20 vs 4/6, p = 1.000) (Table 2).

Disease Evolution and Outcome

114 patients had lung function tests available at 24 months. Overall, the median absolute decline for FVC was − 1.0% and − 4.5% for DLCO at this timepoint. Patients with short TL displayed a faster FVC decrease at 2 years compared to individuals with normal TL (− 4.0 vs + 3.0% predicted, p = 0.005). Similarly, DLCO decline was more important in short TL patients (− 7.0 vs − 3.0% predicted, p = 0.023) (Fig. 2)A, B and E, F). Of note, patients with very short TL tended to have a faster decline than patients with TL between P1 and P10 (− 5.0 vs − 1.0% predicted, p = 0.058). This was not observed for DLCO (− 8.00 vs − 7.0%, p = 0.919) (evolution over time Fig. 2C, D and G, H). The presence of FPF was not associated with higher lung function decline in our data (p = 0.54 for FVC and p = 0.44 for DLCO). In the small group of patients with an identified TRG mutation there was no difference in FVC or DLCO evolution at 24 months, in comparison with other patients, including in the subanalysis of FPF patients with and without the presence of variants (p = 0.95 and p = 0.29).

Table 2 Clinical characteristics of patients with very short and short TL

	TL < p1 n = 42	TL between p1-p10 n = 32
Age at diagnosis, years (median (IQR))	67 (63–72)*	71 (67–75)*
Sex, male (n (%))	33 (79)	28 (88)
Smoking status, ever/never (n(%))	32 (76)/10 (24)	21 (66)/11 (34)
Pack years, number (n(%))	18 (10–39)	25 (20–40)
UIP pattern on HRCT, UIP, pUIP, indUIP, alt (n(%))	14/10/15/3	10/13/8/1
Lung biopsy performed (n(%))	19 (45)	9 (28)
TRG variant screening (n(%))	20 (48)*	7 (22)*
Identification of TRG mutation(n(%))	10 (50)	4 (57)
Baseline FVC, %PV (median (IQR)	84 (73–95)	81 (71–96)
Baseline DLCO %PV (median (IQR)[#]	57 (46–73)	51 (44–70)

All continuous data are expressed as median and interquartile range. A Mann Whitney U test was used for between group comparison of continuous variables. X^2 or when appropriate Fisher exact test were used for intergroup comparison of categorical variables. * $p < 0.05$. TL: telomere length, p10: percentile 10, p1: percentile 1, IQR: interquartile range, UIP: usual interstitial pneumonia, HRCT: high resolution CT, pUIP: probable UIP, indUIP: indeterminate for UIP, alt: alternative pattern, TRG: telomere related genes, FVC: forced vital capacity, DLCO, diffusion capacity of the lung for carbon monoxide, PV: predicted values. #: missing data n = 2

At the time of the analysis, 25/143 (17%) patients were dead or had undergone lung transplantation. Patients with short telomeres had a worse transplant-free survival ($p = 0.05$, Fig. 3A). No difference in survival was observed between very short and short telomeres ($p = 0.11$). Mortality rate was similar in FPF and sporadic fibrosis ((5/30 (16.66%) vs 20/113 (17.69%), $p = 1.00$). Of note, all deaths or transplantation in the FPF subgroup occurred in patients with short telomeres. There was a significant difference in transplant-free survival between patients with GAP score stage I, II and III ($P = 0.0013$) (Fig. 3B). Interestingly, within the GAP score stage I group, the presence of short TL implied a significative worse transplant-free survival (p 0.04). This trend was also found in the GAP stage II and III group but was not statistically significant (Fig. 3C).

Discussion

In this multicentric cohort study, the telomere length of 143 consecutive unselected IPF patients was measured by flow-FISH. Half of the cohort had short and one-third very short TL. Notably, patients with very short TL were diagnosed at a younger age and all class 4–5 variants in TRG were found in individuals with short or very TL. Finally, short TL patients displayed an increased mortality compared to patients with normal TL, despite similar baseline severity markers such as FVC and DLCO.

The implication of shortened telomeres and telomere biology disorders is being increasingly recognized in IPF. Indeed, short telomeres have been reported in up to 60% of cases [9] and 10% of patients possess a rare variant in a gene related to telomere maintenance [19]. The importance of underlying genetic mechanisms is illustrated by the fact that variants in telomere related genes are the most commonly identified in both sporadic and familial IPF patients [20]. Nonetheless, the presence of short telomeres is by itself sufficient to favour the development of IPF as relatives of patients with a known variant in TRG have been shown to develop pulmonary fibrosis, even in the absence of the incriminated variant [21]. In line with this, all (likely) pathogenic variants were identified in the short and very short TL group in our cohort. In the meantime, in almost half of tested patients with short TL, no variant of interest could be documented. This suggests either unknown genetic mechanisms or phenocopies. In the latter case, it is still unclear whether these patients have inherited short telomeres from a parent or if additional environmental factors could have played a role.

We showed that patients with short TL had a faster disease evolution and increased mortality. Short TL have been associated with an increased respiratory decline and worse prognosis [22–24], hypothetically due to faster AEC2 progenitor function exhaustion and senescence, promoting a profibrotic environment. Indeed, our current understanding of IPF pathogenesis places AEC2 stem cell exhaustion at the centre of the disease [25] and AEC2 specific TL alterations limit renewal and promotes senescence of these cells, resulting in increased susceptibility to second hit fibrotic stimuli [7, 26]. In addition, leukocyte telomere length correlate with local AEC2 TL in sporadic IPF [27], potentially reflecting the replicative potential of the latter. Adding to this, a post-hoc analysis of the PANTHER-IPF and ACE trials based on available TL revealed an increased mortality in patient with short telomeres and exposure to immune suppression

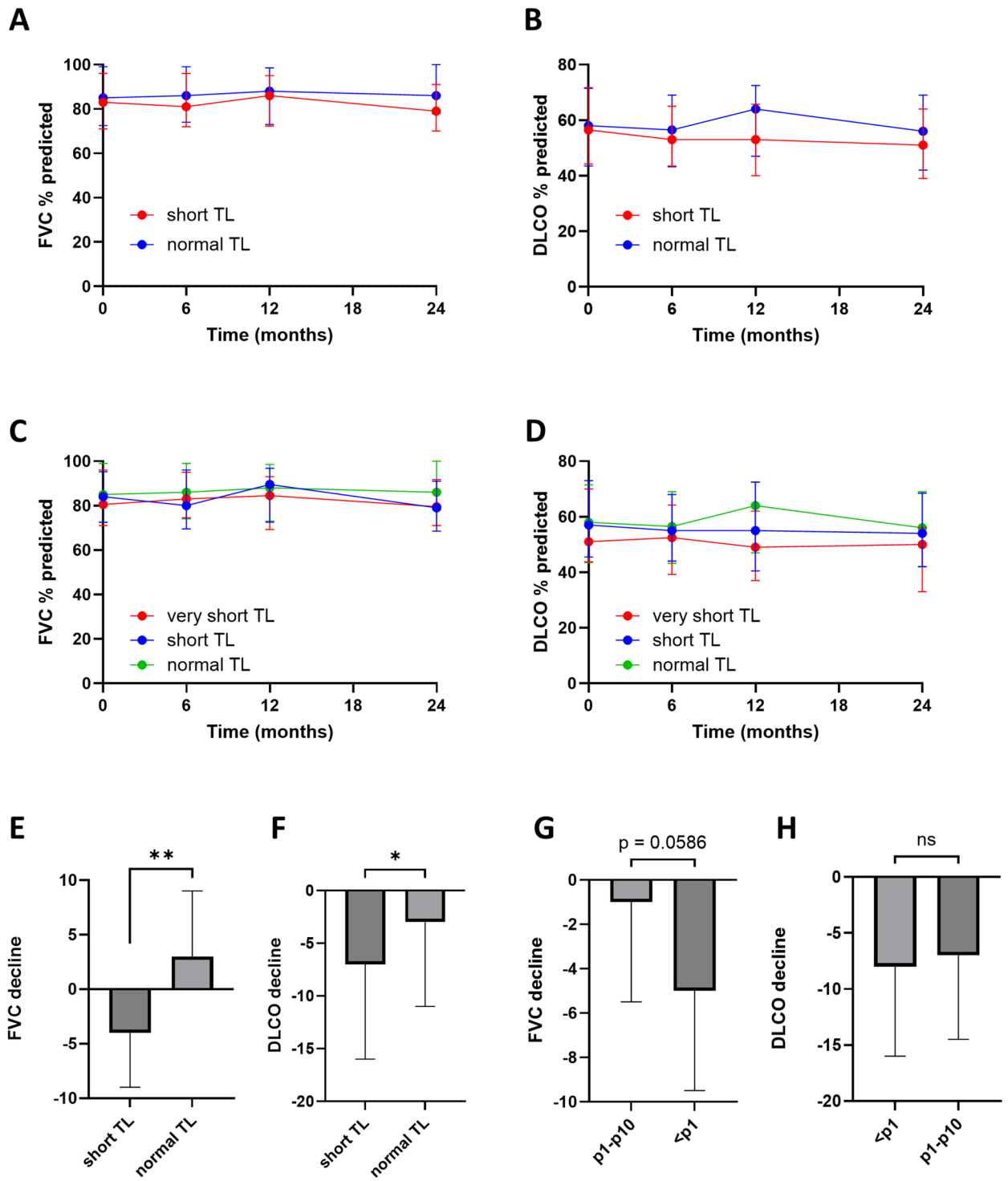

Fig. 2 Lung function evolution over time. **A** Evolution of the forced vital capacity (FVC) over time between patients with short and normal TL. **B** Evolution of the diffusion capacity of the lungs for carbon monoxide (DLCO) over time between patients with short and normal TL. **C** FVC evolution over time based on telomere length. **D** DLCO evolution over time based on telomere length. **E** FVC evolution between 0 and 24 months between patients with short and normal TL. **F** DLCO evolution between 0 and 24 months between patients with short and normal TL. E–F: Between group comparison was performed using a Mann Whitney U test. *p < 0.05, **p < 0.01. FVC: forced vital capacity, DLCO: diffusion capacity of the lungs for carbon monoxide, TL: telomere length

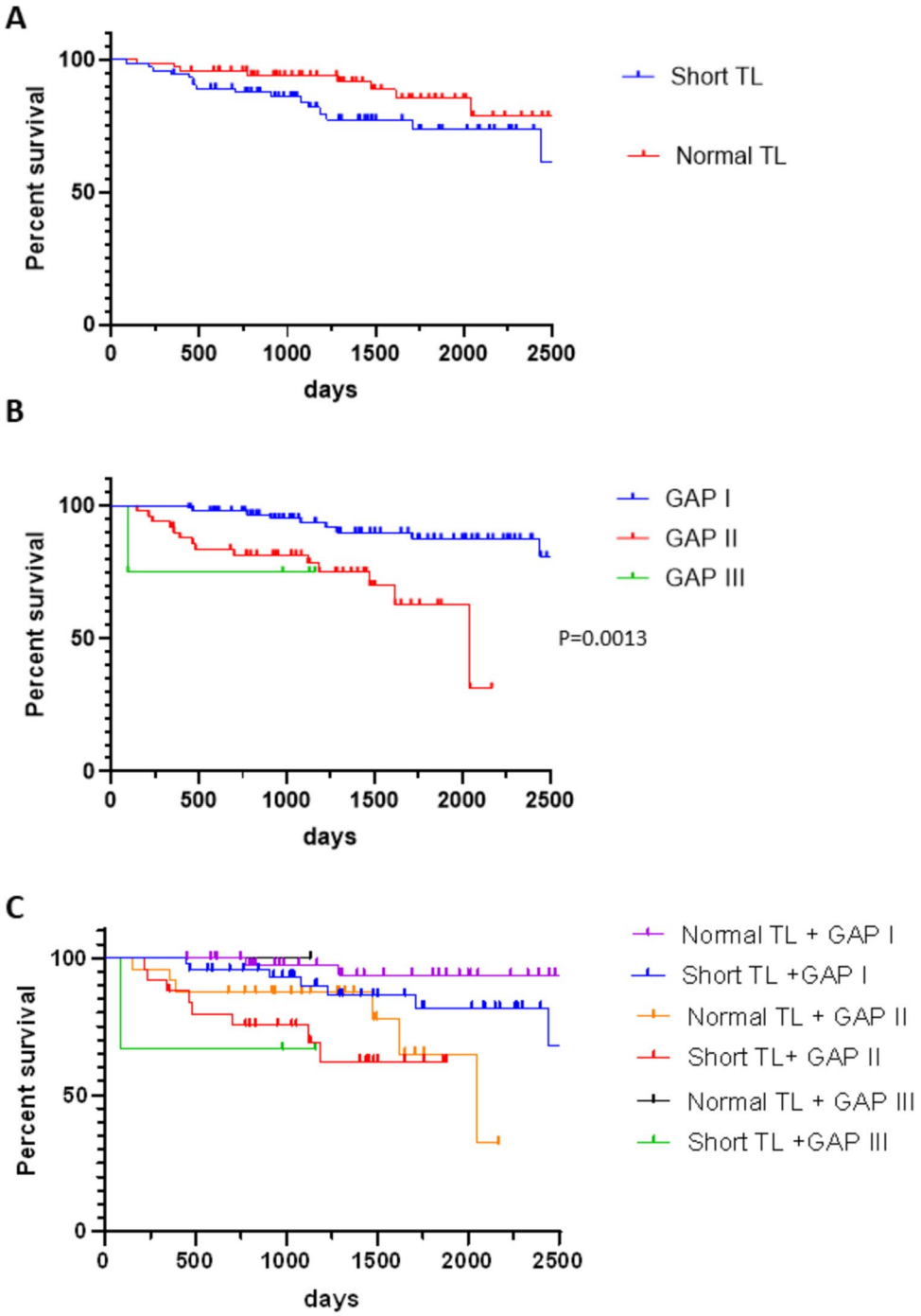

Fig. 3 Transplant-free survival of the cohort. **A** Transplant-free survival of patients with short and normal telomere length. **B** Transplant-free survival of patients according to GAP index. **C** transplant-free survival according to both GAP index and telomere length. Log-rank test

[9], advocating for a role of myeloid cell dysfunction behind this observation.

Moreover, we show a significant difference in survival in patients with GAP 1 staging (Fig. 3C), illustrating the influence of TL on the prognosis of this subpopulation.

Short telomeres are linked with an increased lung function decline [9] and a correlation between telomere length and mortality has been reported in IPF, showing that shorter TL are associated with a worse prognosis [28]. However, to what extent patients with very short and short TL differ regarding lung function evolution and mortality remains poorly documented. 29% of the patients of our cohort presented with very short telomeres and this subgroup displayed a faster lung function decline, suggesting a worsened disease course. This was not reflected by mortality, possibly due to the small sample size. Notably, these patients were diagnosed at a younger age compared to patients with TL between P1-P10. No other differences in demographic,

genetic or familial characteristics that could have influenced TL were noted. Telomere length has been associated with genetic anticipation and phenotype [29]. This results in earlier disease onset in patients with shorter telomeres, including in pulmonary fibrosis patients [11]. This points to the fact that a certain range exists within which short telomeres will manifest as pulmonary fibrosis and that variations in this range will result in variations in respiratory disease course and age of onset. As such, telomeres length is relevant for the prognosis of patients even in individuals with short telomeres.

Our study has several limitations. First, the design and size hinder definitive conclusions regarding mortality or lung function decline, as it may have missed statistical power to detect differences. Secondly, genetic analysis was performed on indication in short TL patients and variants may have been missed in untested individuals.

In conclusion, short TL is a frequent finding in our unselected IPF population and relates to outcome. The presentation of the disease at diagnosis was similar between patients with or without short TL but disease evolution was accelerated in the short TL group with a higher mortality rate and more severe lung function decline. Furthermore, short telomeres were linked to genetic variants. Finally, patients with very short TL did not display a worse prognosis when compared to patients with TL between p1-p10 but had an earlier onset of disease. Altogether, our study supports the use of TL as a biomarker in IPF management.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00408-025-00830-6.

Author Contributions C.D and T.P.B wrote the manuscript text and prepared Fig. 1–3. A.F. corrected the manuscript and prepared figure S1. T.M. collected and analyzed data. A.D. and M.A. V.D. designed and performed Flow-FISH. A.D.L. performed and provided genetic analyses. B.G. and E.C. centrally reviewed all HRCT. All authors reviewed the manuscript and accepted its final version.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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