EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Guler SA, Kwan JM, Leung JM, *et al*. Functional aging in fibrotic interstitial lung disease: The impact of frailty on adverse health outcomes. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00647-2019).

Functional aging in fibrotic interstitial lung disease: The impact of frailty on adverse health outcomes

Running head: Aging in fibrotic interstitial lung disease

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Take home message: Frailty independently predicts adverse health outcomes in patients with fibrotic ILD; with functional aging as the main driver of most age-related adverse health outcomes there is a need to recognize, prevent, and treat frailty in this population.

Funding: This study was co-funded by the British Columbia Lung Association and InterMune / Hoffmann-La Roche Inc. Neither sponsor had input into the study design, analysis, interpretation of results, or the presentation of findings.

Conflict of interest: SAG, JMK, JML, NK, PGW, and CJR confirm that there are no conflicts of interest associated with this work.

Prior abstract presentation: This work has been presented in the form of two abstracts at the American Thoracic Society (ATS) International Conference 2018 in San Diego, and at the European Respiratory Society (ERS) Congress 2018 in Paris.

ABBREVIATIONS

aTL, absolute telomere length

CI, confidence interval

COPD, chronic obstructive pulmonary disease

Co-FI, comorbidity Frailty Index

CTD, connective tissue disease

DLCO, diffusion capacity of the lung for carbon monoxide

FEV_1, forced vital capacity in one second

FI, frailty index

FVC, forced vital capacity

GAP, Gender Age Physiology

HP, hypersensitivity pneumonitis

HR, hazard ratio

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

IQR, interquartile range

IRR, incidence rate ratios

I&SC-FI, independence and self-care Frailty Index

MAR, medication adverse reactions

SD, standard deviation

SGRQ, St George's Respiratory Questionnaire

WHO, World Health Organization

ABSTRACT

Background: Accelerated biological and functional aging is common in fibrotic interstitial lung disease (ILD); however, their impact on adverse health outcomes has not been evaluated in this population.

Methods: Patients were prospectively recruited from a specialized ILD clinic. Functional aging was determined by the frailty index (FI), and biological age by measurement of absolute telomere length (aTL) from patients' peripheral blood leukocytes. Adverse health outcomes included health-related quality of life (St George's Respiratory Questionnaire), number and length of respiratory and non-respiratory hospitalisations, medication tolerability, and time to death or lung transplantation. Multivariable models were used to determine the risks and rates of adverse health outcomes associated with the FI and aTL.

Results: 540 patients with fibrotic ILD, including 100 with idiopathic pulmonary fibrosis (IPF), provided 749 FI assessments, with 189 patients providing blood samples. The FI was strongly associated with quality of life, rate of hospitalisation, time to hospital discharge, and mortality, including with adjustment for age, sex, disease severity, and IPF diagnosis. Mortality prognostication was improved by the addition of the FI to commonly used clinical parameters and previously validated composite indices. Conversely, aTL was not associated with most adverse health outcomes. The effect of chronological age on outcomes was mediated primarily by the FI and to a lesser extent by aTL.

Conclusions: Functional aging is associated with adverse health outcomes in patients with fibrotic ILD, indicating the need for consideration of the individual functional age into clinical decision-making.

INTRODUCTION

Interstitial lung disease (ILD) is an increasingly common group of inflammatory and fibrotic disorders that damage the lung parenchyma. Fibrotic ILDs are typically associated with exercise limitation, reduced quality of life and early mortality. Many fibrotic ILDs, including idiopathic pulmonary fibrosis (IPF), increase in incidence with age and are thus frequently associated with comorbidities that increase the complexity of management and place substantial burden on the healthcare system.[1-3]

The time-dependent gradual loss of physical and social functioning with aging is typically accelerated in patients with chronic diseases,[4] and many cellular and molecular hallmarks of aging are frequently and prematurely observed in patients with fibrotic ILDs.[5, 6] The accelerated functional aging associated with fibrotic ILD is best represented by the concept of frailty, defined as the accumulation of age- and health-related deficits across physical, psychological, and social systems.[4, 7-9] This diminished physiological reserve and increased vulnerability to minor stressors is common in fibrotic ILD,[10-12] and may expose these patients to adverse health outcomes. Frailty has been associated with a higher risk of death in the general population,[4, 9] in patients with chronic obstructive pulmonary disease (COPD),[13] and in lung transplant candidates.[14] However, the risks associated with frailty as a proxy of accelerated functional aging, and different impacts of functional, biological and chronological aging in patients with fibrotic ILD have not been evaluated.

The goal of this study was therefore to determine the impact of functional aging (i.e., frailty) on mortality, hospitalisations, and quality of life in a large cohort of patients with fibrotic ILD. We used peripheral blood leukocyte telomere length as a proxy of biological aging to further determine the specific role of functional aging compared to biological and chronological aging. Our pre-specified central hypothesis was that frailty would independently predict adverse health outcomes in fibrotic ILD, thus indicating the central importance of functional aging in the management of these patients.

METHODS

Study population and measurements

Consecutive patients with a multidisciplinary diagnosis of fibrotic ILD were recruited from an outpatient ILD referral centre between July 2014 and July 2017, including patients with idiopathic pulmonary fibrosis (IPF),[15] chronic hypersensitivity pneumonitis (HP),[16] unclassifiable ILD, and connective tissue disease (CTD)-associated ILD.[17] All patients provided informed written consent (UBC ethics board approval H10-03099).

Functional aging: The Frailty Index

Frailty, representing functional aging, was measured using a self-reported Frailty Index (FI) consisting of 42 deficits, including 19 comorbidities and 23 deficits related to independence and self-care. Patients confirmed or denied the presence of each equally weighted deficit, as previously described.[18] The FI is calculated as the proportion of items present divided by the total number of surveyed items, expressed as a continuous variable between 0 and 1. Surveyed deficits without a patient response were removed from the denominator (1.5% of all surveyed items). Frailty was defined as FI >0.21.[4] Data from the Canadian Study of Health and Aging show a submaximal limit of the FI of 0.65 (+/- 0.02) in a general outpatient population, beyond which mortality is imminent.[19] We previously demonstrated that the FI has good internal consistency in fibrotic ILD and that frailty is more prevalent in patients with fibrotic ILD than in the general population.[10] The items within the FI were subcategorized into 19 items related to comorbidities (Co-FI), and 23 items related to independence and self-care (I&SC-FI). The FI was completed at study entry, including both incident and prevalent diagnoses of ILD, and during follow-up when patients returned for routine clinical assessments. FI that were completed within 6 months of a preceding FI were excluded from analysis, in order to avoid overlapping observation periods.

Biological aging: Leukocyte telomere length

Blood leukocyte telomere length was measured in a random subgroup of consecutively recruited patients who consented to donate blood samples. We applied a modified version of the Cawthon method for measurement of absolute telomere length (aTL) using quantitative real-time polymerase chain reaction.[20, 21] A detailed description is provided in the supplement.

Outcome assessments

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ) without any modification. This 50-item patient-reported questionnaire was specifically developed for respiratory diseases,[22] is frequently used in patients with ILD, and has recently been validated in connective tissue disease-associated ILD.[23, 24] The SGRQ includes three domains relating to symptoms, activity, and impact, as well as a total score that ranges from 0-100 with a higher score indicating worse quality of life. Non-elective respiratory-related hospitalisations, non-respiratory-related hospitalisations, and cumulative number of days admitted to hospital within 6 months of each frailty assessment were identified from the medical record. Patients completing more than one frailty assessment contributed multiple non-overlapping 6-month follow-up intervals during the study period. Time to death, lung transplantation, or censoring was calculated from the date of the first frailty assessment. The medical record was used to identify adverse effects related to prevalent ILD pharmacotherapy that occurred within 6 months of each frailty assessment. Medication adverse reactions (MAR) were defined according to the World Health Organization (WHO) as an unintended or noxious response to a drug that occurs at doses normally used in humans.[25] MARs were specified as effects that resulted in a dose reduction, purposeful treatment interruption for longer than one day, or treatment discontinuation for more than 14 days.[25]

Other measurements

Demographics and baseline characteristics were collected from the clinical record, including age, sex, body mass index, and smoking history. Pulmonary function tests were performed using established protocols.[26, 27] All clinical measurements were completed within 3 months of the frailty assessment.

Statistical analysis

Data structure was hierarchical with multiple FI and covariate measurements per patient at time intervals of 6 months or more. The primary mortality endpoint was time to the composite of death or lung transplantation. Other outcomes were assessed within the 6-month time periods after every

FI assessment. Time to death or lung transplantation and time to hospital discharge were each analysed using Cox proportional hazards regression models. Discrimination was measured using the Harrell's C-statistic. In a pre-specified sensitivity analysis we used competing risk regression according to Fine and Gray,[28] with death and lung transplantation as competing risks. Rate of hospitalisations, probabilities for MAR, and associations with SGRQ were modelled using generalized mixed effects models accounting for intra-patient correlation with random intercepts. Fixed effects included FI, TL, and potential confounders with either conceptual importance (age, sex) or a statistically relevant relationship to the outcome. These models were fitted for linear, binomial and Poisson distribution families according to the outcomes of interest. Mediation of the effect of chronological age on adverse health outcomes by either functional age (FI) or by biological age (aTL) was explored with causal mediation analysis (CMA). Estimates for the average causal mediation effect/average total effect for an increase in chronological age by one year were reported. A directed acyclic graph is provided in the supplement (Figure S1). Model specification, assumption testing and specific statistical programs used are reported in the supplement. A two-sided $p<0.05$ was used to indicate statistical significance for all comparisons. Data were analyzed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[29]

RESULTS

Patient characteristics

The 540 patients provided a total of 749 frailty assessments with a median (IQR) interval of 10.8 (6.2-17.7) months between assessments in patients who completed more than one frailty questionnaire (**Table 1**). Diagnoses included IPF (n=100), systemic sclerosis-associated ILD (n=109), other CTD-ILD (n=118), chronic HP (n=47), and 39 with other ILDs. A confident diagnosis was unable to be assigned for 127 patients who were designated as unclassifiable ILD. At baseline, 42% of men and 56% of women were classified as frail. The median (IQR) FI for the entire cohort was 0.214 (0.095-0.333), the Co-FI was 0.158 (0.052-0.211), and the I&SC-FI was 0.261 (0.087-0.435). Women had accelerated

functional aging with higher frailty scores compared to men, as did patients with non-IPF ILDs compared to patients with IPF (**Table 2**).

Health-related quality of life

Frailty severity was correlated with worse quality of life on unadjusted analysis and with adjustment for age, sex, ILD severity, and IPF diagnosis (**Table 3**). This was present for pairwise associations of all frailty measures (FI, Co-FI, I&SC-FI) with all SGRQ domains.

Hospitalisations

There were 231 non-elective hospitalisations within the 749 observation periods from the 540 patients, including 131 respiratory-related hospitalisations. Over the entire study period, 459 patients had no hospitalisations and 81 patients had between 1 and 5 hospitalisations. The median cumulative number of days admitted to hospital within 6 months of frailty assessment was 5 (2-14) among those periods with at least one hospitalisation. Patients with more severe frailty had a higher rate of all-cause and respiratory-related hospitalisations and longer time to hospital discharge on unadjusted and adjusted analysis, with these associations primarily driven by the I&SC-FI component of frailty (**Table 3** and **Figure 1**). On unadjusted analysis, frail patients had more than double the rate of all-cause and respiratory-related hospitalisations with significantly greater risk for prolonged hospital stay. All but the association with respiratory-related hospitalisations remained statistically significant on adjusted analysis.

Survival

Over the median follow-up time of 17 (9.2-26.7) months, 81 patients died and 14 patients underwent lung transplantation. Patients with advanced functional aging hence classified as frail had significantly worse 1-/2-/3-year transplant-free survival of 86%/77%/73% compared to non-frail patients (94%/91%/87%, $p<0.001$; **Figure 2**). Higher FI and I&SC-FI were associated with time to death or transplant on unadjusted analysis and with adjustment for age, sex, IPF diagnosis, and ILD severity (**Table 3**), and with adjustment for the composite Gender Age Physiology (GAP)-ILD Index (data not shown).[30] The prognostic ability of the models increased substantially when FI was

added to age and sex, with a marginal and probably clinically non-relevant increase of the C-index when FI was added to a multivariate model including age, sex, ILD severity, and IPF diagnosis (**Table 4**). Consistent results were obtained using a pre-specified sensitivity analysis that considered death and lung transplantation as competing risks. The submaximal limit of the FI was 0.67, corresponding to the 99th-percentile. Stratification by IPF and CTD-ILD diagnoses revealed largely unchanged findings (data not shown).

Medication adverse reactions

The 239 patients (44%) treated with ILD-specific medications had a higher FI (0.244 versus 0.191, p=0.005) compared to untreated patients. In patients already on ILD-specific medication at the time of assessment, future dose reductions and treatment discontinuation both occurred in 3% of immunosuppressive treatments within 6 months of the FI assessment, whereas 12% of anti-fibrotic therapies resulted in MAR leading to treatment discontinuation. Within the subsequent 6-month observation period after frailty assessment, patients classified as frail were more likely to have a MAR resulting in dose reductions on unadjusted analysis (odds ratio 11.3, 95%-CI 1.01-127, p=0.049); however, this analysis was underpowered and this association lost statistical significance with adjustment for age, sex, ILD severity, and IPF diagnosis (odds ratio 7.03, 95%-CI 0.62-79.8, p=0.12).

Impact of telomere length on outcomes

Baseline characteristics of the telomere subgroup were similar to the full cohort (**Table S2**). Absolute TL as a proxy of biological aging showed no correlation with functional aging (FI) in the sub-cohort of the 189 patients who had provided a blood sample at the time of frailty assessment (r=0.04, p=0.57), although there was moderate correlation of chronological and biological age (r=-0.36, p<0.001). Absolute TL did not predict survival or quality of life on unadjusted analysis; however, there was a 6% (IRR 95%-CI 0.99-1.12, p=0.056) and 9% (IRR 95%-CI 1.01-1.17, p=0.03) higher rate of all-cause and respiratory-related hospitalisations for each 10kpb/genome decrease in aTL. These associations were not maintained with adjustment for age and sex (**Table 5**).

Causal mediation analysis

An exploratory causal mediation analysis showed that the overall effect of chronological age on 2-year survival (per 10-year increase OR 2.41 [95%-CI 1.37-7.09], p=0.01) was mediated largely by functional age (FI indirect/total effect 53%), whereas a model including aTL as mediator showed that a smaller fraction of the effect of chronological age on outcomes was mediated by biological age (aTL indirect/total effect 31%). Similarly, the increased rate of all-cause hospitalisations in older patients (per 10-year increase IRR 1.35 [95%-CI 1.04 to 1.77], p=0.03) was mainly mediated by functional age (FI indirect/total effect 43%), and to a lesser extent by biological age (aTL indirect/total effect 22%). Conversely, the effect of chronological age on respiratory-related hospitalisations (per 10-year increase IRR 1.54 [95%-CI 1.08 to 2.26], p=0.02) was primarily mediated by biological age (aTL indirect/total effect 45% versus FI indirect/total effect 13%). Robustness of the models to unmeasured confounding between the mediator and the outcome was confirmed as previously suggested and described in the supplementary methods.[31]

DISCUSSION

We evaluated chronological, functional, and biological aging in this large prospective cohort of patients with fibrotic ILD to show that frailty predicts adverse health outcomes and is a clinically relevant concept representing functional age in this population. Beyond its significant association with mortality, we show that frailty is associated with worse quality of life, a twofold higher rate of hospitalisations, and longer hospital stay. Although underpowered, our findings also suggest that frailty may predict medication side effects and intolerance. Overall it appears that in this cohort, functional aging is prognostically more important than biological aging.

Multi-dimensional mortality risk prediction models that consider demographic and lung function have a better discriminative ability compared to single predictor variables in patients with ILD;[30, 32-34] however, these are still suboptimal. There is increasing evidence on the impact of comorbidities and accelerated biological aging on survival of patients with ILD,[35, 36] and measures of overall health state such as frailty may provide additional prognostic information. Using several

clinically relevant outcomes, this is the first study showing that functional aging provides prognostic information beyond that of commonly used clinical parameters in patients with ILD. A FI of 0.65 is the submaximal limit to the proportion of deficits that can be accumulated by elderly community-dwelling individuals before death is very likely imminent.[19] We similarly show the 99% limit to the FI was 0.67 in our younger cohort, consistent with previous observations that the FI limit is independent of chronological age. Combined with the reduced medication tolerance in frail patients, this finding suggests that patients approaching this submaximal limit should have their goals of care carefully reassessed, potentially changing to a palliative strategy that prioritizes symptom management rather than continuation of potentially toxic ILD pharmacotherapy.

The role of aging as a complex biosocial process is increasingly recognised in ILD.[6] To our knowledge, this is the first study investigating the clinical importance of functional, chronological, and biological aspects of aging in a single cohort of patients with fibrotic ILD, showing that functional aging represented by the FI is overall more important than chronological and biological aging for prognostication in this population. We explored potential causal pathways mediated by functional and biological aging to show that functional aging (*i.e.*, frailty) drives more than 50% of the overall age-effect on mortality, whereas biological aging (*i.e.*, aTL) accounts for about 30%. Similarly, functional aging was the primary driver of all-cause hospitalisations, while biological aging was the main driver of respiratory-related hospitalisations. These findings suggest that respiratory-related hospitalisations may be predominantly caused by biological reasons such as ILD worsening (e.g., exacerbation, progressive hypoxemia, chronic inflammation catabolic metabolism), whereas the reasons for all-cause hospitalisations are usually more complex (e.g., decompensation of the social support system).

Causal mediation analysis requires some assumptions that we addressed in sensitivity analyses, but there are no cut-off values to judge the robustness these analyses, and inferences form these models need to be confirmed in future studies. We had a relatively small size of some patient subgroups which limited the power of subgroup analyses, particularly for telomere length analyses;

however, our diverse cohort also allows generalization to a larger population of patients with fibrotic ILD. Despite the growing awareness of accelerated functional aging as a public health problem, there is no agreement on a single definition of frailty.[37] Based on the importance of physical functionality for independence in daily living, the Fried frailty phenotype for example includes a measure of physical performance.[8] We used the FI, which is a simple measure that does not include any physical testing,[4, 18, 38] suggesting that physicians can easily apply many of these concepts in patient care. Self-reported tools such as the FI inherently incorporate a patient's self-efficacy and perspective on his/her own deficits. This reliance on individual reporting potentially introduced heterogeneity to our findings, but our large study cohort nevertheless allowed demonstration of statistically significant associations of functional aging with adverse health outcomes.

CONCLUSION

This novel identification of functional aging as the main driver of quality of life and most age-related adverse outcomes in fibrotic ILD emphasizes the importance of recognizing, preventing, and treating frailty in this population. These findings suggest the need for integration of the individual functional age in clinical decision-making and prognostication in these patients. Future studies are needed to evaluate the utility of frailty in clinical decision algorithms and to investigate the effectiveness of specific treatment approaches to frailty in patients with fibrotic ILD.

ACKNOWLEDGEMENTS

Funding: This study was co-funded by the British Columbia Lung Association and InterMune / Hoffmann-La Roche Inc. Neither sponsor had input into the study design, analysis, interpretation of results, or the presentation of findings.

Authors' contributions: CJR takes responsibility for the content of the manuscript, including the data and analysis and is guarantor of this paper. SAG and CJR contributed to the conception and design of the study, and acquisition, analysis, and interpretation of the data. JMK, JML, NK, and PGC contributed to the acquisition and interpretation of the data. All authors revised the manuscript for important intellectual content and provided final approval of the version to be published.

The authors would like to acknowledge the patients of the St. Paul's Hospital ILD Clinic who allow us to conduct this research in an effort to improve the lives of patients with ILD.

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TABLES

Table 1. Baseline characteristics of men and women with fibrotic interstitial lung diseases.

	Men (n=232)	Women (n=308)
DEMOGRAPHICS		
Age, years	67.4 (10.2)	62.8 (12.4)
Body mass index, kg/m^2	28.5 (5.0)	27.3 (6.0)
Ever-smoker	128 (55%)	144 (47%)
Smoked pack-years*	24.2 (9.5-37)	16.0 (1.8-25)
ILD SEVERITY		
FVC, %-predicted	73.0 (19.0)	75.1 (22.1)
FEV_1, %-predicted	74.9 (18.3)	77.1 (23.3)
DLCO, %-predicted	52.9 (18.8)	52.9 (18.7)
QUALITY OF LIFE		
SGRQ, total	42.3 (22.8)	43.3 (22.2)
SGRQ, activity	53.3 (26.6)	58.1 (23.6)
SGRQ, symptom	51.2 (23.2)	48.0 (24.2)
SGRQ, impact	32.8 (22.8)	33.8 (23.5)

Data are presented as mean (standard deviation), median (interquartile range), or frequency (percentage).

*in ever-smokers

Abbreviations: DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; FEV_1, forced vital capacity in one second; FVC%, forced vital capacity %-predicted; ILD, interstitial lung disease; SGRQ, St. George's Respiratory Questionnaire.

Table 2. Frailty and telomere length in men and women with IPF and non-IPF fibrotic interstitial lung diseases.

	Men (n=232)	Women (n=308)	IPF (n=100)	Non-IPF ILD (n=440)
Frailty Index	0.167 (0.071-0.286)	0.238 (0.120-0.358)	0.167 (0.092-0.288)	0.214 (0.095-0.333)
Co-FI	0.105 (0.053-0.211)	0.158 (0.105-0.263)	0.111 (0.097-0.211)	0.158 (0.055-0.214)
I&SC-FI	0.217 (0.043-0.384)	0.304 (0.087-0.478)	0.174 (0.077-0.391)	0.261 (0.087-0.435)
Frail (FI >0.21)	98 (42%)	174 (56%)	39 (39%)	233 (53%)
Prefrail (FI 0.1-0.21)	58 (25%)	61 (20%)	28 (28%)	91 (21%)
Absolute telomere length, kbp/genome*	171.1 (45.4)	185.6 (45.8)	163.3 (40.7)	183.2 (46.7)

Data are presented as mean (standard deviation), median (interquartile range), or frequency (percentage).
* Absolute telomere length was calculated for a subgroup of patients with available blood samples (sample size: men=87, women=102, IPF=41, non-IPF ILD=148)

Abbreviations: Co-FI, comorbidity Frailty Index; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; I&SC-FI, independence and self-care Frailty Index

Table 3. Association of frailty with outcomes in fibrotic ILD.

	Unadjusted analysis		Adjusted for age, sex, FVC%, DLCO%, IPF	
	Coeff/IRR/HR (95%-CI)	p-value	Coeff/IRR/HR (95%-CI)	p-value
HEALTH-RELATED QUALITY OF LIFE (SGRQ)				
Frailty Index	7.01 (6.04-7.98)	<0.0001	5.83 (4.81-6.84)	<0.0001
Co-FI	3.49 (2.25-4.72)	<0.0001	4.00 (2.79-5.22)	<0.0001
I&SC-FI	5.25 (4.58-5.92)	<0.0001	4.41 (3.68-5.15)	<0.0001
Frail	21.6 (18.0-25.4)	<0.0001	18.0 (14.1-21.7)	<0.0001
Rate of ALL-CAUSE HOSPITALISATIONS				
Frailty Index	1.03 (1.02-1.04)	<0.0001	1.03 (1.01-1.04)	<0.0001
Co-FI	1.02 (1.00-1.03)	0.01	1.03 (1.01-1.04)	0.003
I&SC-FI	1.02 (1.01-1.02)	<0.0001	1.02 (1.01-1.03)	0.0001
Frail	2.25 (1.38-3.47)	<0.0001	1.97 (1.32-3.06)	0.002
Rate of RESPIRATORY-RELATED HOSPITALISATIONS				
Frailty Index	1.03 (1.01-1.04)	0.0003	1.02 (1.01-1.04)	0.02
Co-FI	1.01 (0.99-1.03)	0.24	1.02 (1.00-1.04)	0.06
I&SC-FI	1.02 (1.01-1.03)	<0.0001	1.01 (1.00-1.03)	0.03
Frail	2.01 (1.25-3.34)	0.003	1.63 (0.79-2.43)	0.09
TIME TO HOSPITAL DISCHARGE				
Frailty Index	1.02 (1.00-1.03)	0.005	1.02 (1.00-1.03)	0.009
Co-FI	1.01 (0.99-1.02)	0.48	1.01 (0.99-1.03)	0.19
I&SC-FI	1.01 (1.01-1.02)	0.001	1.01 (1.00-1.02)	0.004
Frail	1.56 (1.55-1.57)	0.01	1.35 (1.32-1.38)	0.048
TIME TO DEATH				
Frailty Index	1.03 (1.02-1.04)	<0.0001	1.02 (1.00-1.04)	0.02
Co-FI	1.01 (0.99-1.02)	0.46	1.02 (0.99-1.04)	0.26
I&SC-FI	1.03 (1.02-1.04)	<0.0001	1.02 (1.00-1.03)	0.02
Frail	2.64 (2.31-3.02)	<0.0001	1.77 (1.50-2.08)	0.03

Estimates are per 0.01-unit change in FI, except for health-related quality of life where the coefficient represents the change in SGRQ per square root change in FI. Frail is defined as FI >0.21.
Abbreviations: CI, confidence interval; DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; Co-FI, comorbidity Frailty Index, FVC%, forced vital capacity %-predicted; HR, hazard ratio; IPF, diagnosis of idiopathic pulmonary fibrosis; IRR, incidence rate ratio; I&SC-FI, independence and self-care Frailty Index; SGRQ, St George's Respiratory Questionnaire.

Table 4. Discrimination of survival models for established mortality risk factors with the addition of frailty.

		FI (SE)	Co-FI (SE)	I&SC-FI (SE)
Unadjusted	-	0.679 (0.028)	0.528 (0.032)	0.709 (0.026)
Adjusted				
- Age, sex	0.648 (0.028)	0.718 (0.028)	0.650 (0.028)	0.756 (0.026)
- Age, sex, FVC, DLCO	0.853 (0.021)	0.860 (0.021)	0.853 (0.022)	0.866 (0.020)
- Age, sex, FVC, DLCO, IPF diagnosis	0.857 (0.021)	0.861 (0.020)	0.857 (0.021)	0.866 (0.020)

Data shown are optimism-corrected estimates of the Harrell's C-index, obtained by bootstrap resampling with 200 repetitions.
Abbreviations: DLCO%, diffusion capacity for carbon monoxide %-predicted; Co-FI, comorbidity frailty index, FI, frailty index; FVC%, forced vital capacity %-predicted; IPF, diagnosis of idiopathic pulmonary fibrosis; I&SC-FI, independence and self-care frailty index.

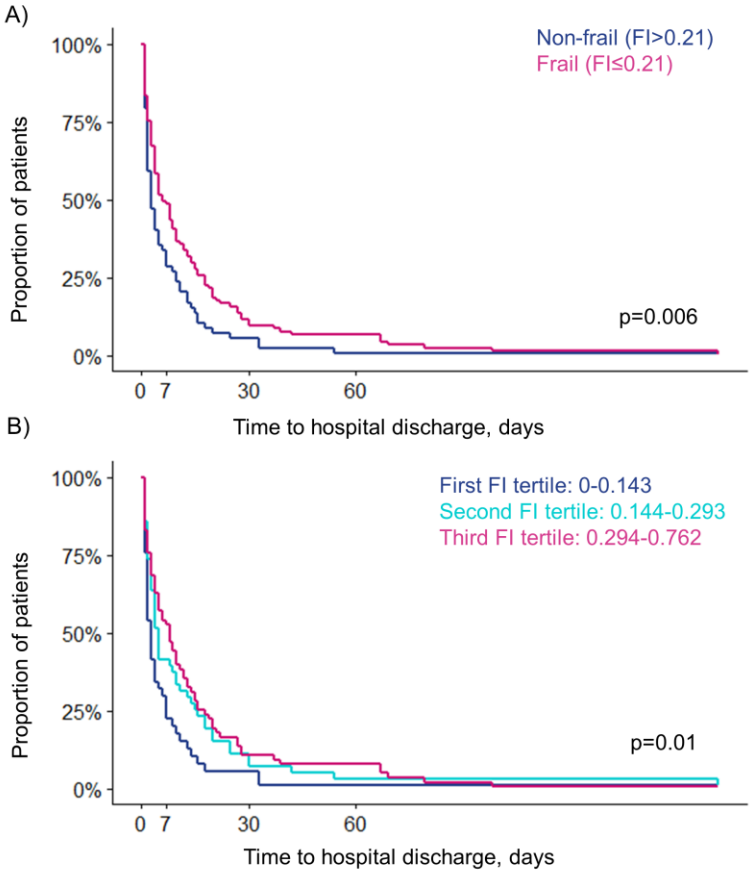
Table 5. Absolute telomere length and risk of mortality, rate of hospitalisations, and quality of life.

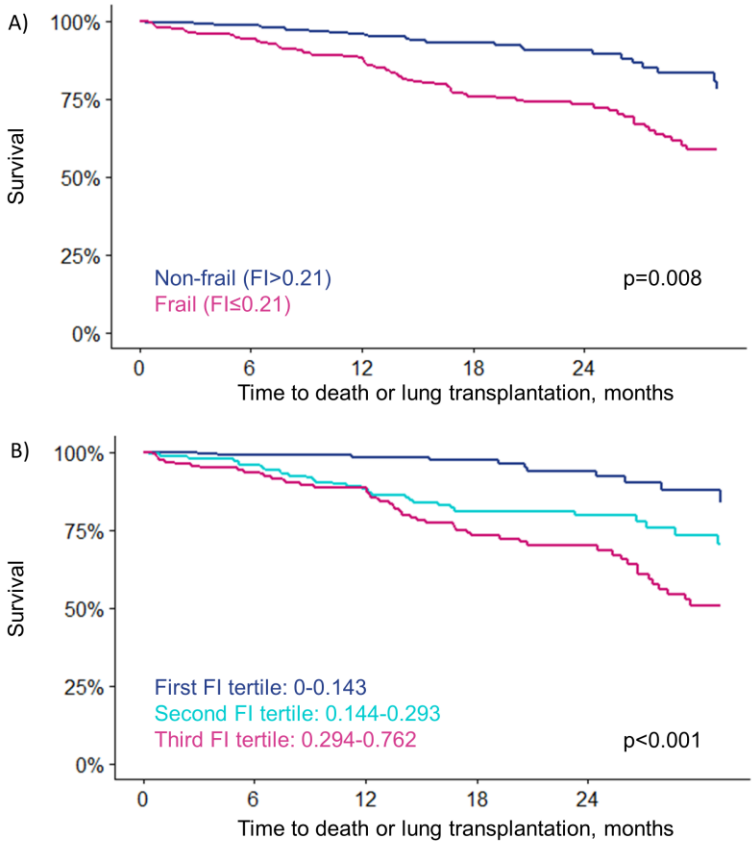
	Unadjusted analysis		Adjusted for age and sex	
	HR/IRR/Coeff (95%-CI)	**p-value**	**HR/IRR/Coeff (95%-CI)**	**p-value**
MORTALITY	0.92 (0.80 to1.04)	0.21	0.96 (0.83 to 1.12)	0.60
ALL-CAUSE HOSPITALISATIONS	0.94 (0.88 to 1.01)	0.06	0.96 (0.89 to 1.03)	0.25
RESPIRATORY-RELATED HOSPITALISATIONS	0.91 (0.83 to 0.99)	0.03	0.99 (0.98 to 1.01)	0.19
TIME TO HOSPITAL DISCHARGE	1.01 (0.94 to 1.05)	0.83	0.99 (0.92 to 1.06)	0.70
HEALTH-RELATED QUALITY OF LIFE (SGRQ)	0.27 (-0.50 to 1.04)	0.49	0.31 (-0.53 to 1.16)	0.47

Data shown are per 10kbp/genome change in telomere length.
Abbreviations: CI, confidence interval; DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; Co-FI, comorbidity Frailty Index, FVC%, forced vital capacity %-predicted; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; IRR, incidence rate ratio.

FIGURES

Figure 1. Time to hospital discharge in non-frail and frail patients (A), and by tertiles of the Frailty Index (B).
*Survival curves from Cox proportional hazard models adjusting for age and sex.
Figure 2. Survival in non-frail and frail patients (A) and by tertiles of the Frailty Index (B).
*Survival curves from Cox proportional hazard models adjusting for age and sex.


A)
Non-frail (FI>0.21)
Frail (FI≤0.21)
Proportion of patients
100%
75%
50%
25%
0%
p=0.006
0
7
30
60
Time to hospital discharge, days
B)
First FI tertile: 0-0.143
Second FI tertile: 0.144-0.293
Third FI tertile: 0.294-0.762
Proportion of patients
100%
75%
50%
25%
0%
p=0.01
0
7
30
60
Time to hospital discharge, days


A)
100%
75%
50%
25%
0%
Survival
Non-frail (FI>0.21)
Frail (FI≤0.21)
p=0.008
0
6
12
18
24
Time to death or lung transplantation, months
B)
100%
75%
50%
25%
0%
Survival
First FI tertile: 0-0.143
Second FI tertile: 0.144-0.293
Third FI tertile: 0.294-0.762
p<0.001
0
6
12
18
24
Time to death or lung transplantation, months

Supplement

Functional aging in fibrotic interstitial lung disease: The impact of frailty on adverse health outcomes

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METHODS

Measurement of blood leukocyte telomere length

Absolute telomere length as a marker of biological and cellular aging was measured in peripheral blood leukocytes from a sub-cohort of patients with fibrotic ILD. Studies comparing telomere attrition in different tissues have shown that telomere length correlates well between blood leukocytes and lung parenchyma, and that the rate of telomere attrition is consistent across organ systems within individual patients, suggesting that there is an intra-individual synchrony of telomere length in somatic tissues.[1,2]

A modified version of the Cawthon method for relative measurement of telomere length using quantitative real-time polymerase chain reaction and introduction of an oligomer standard was applied.[3,4] Genomic DNA was isolated from peripheral blood buffy coat using the QIAamp DNA blood mini kit (Qiagen, Toronto, Canada). Samples underwent only one freeze-thaw cycle before DNA extraction. Standard curves were generated from known quantities of synthesized oligomers of telomere DNA [TTAGGG repeated 14 times] and single copy gene (36B4) DNA [CAGCAAGTGGGAAGGTGTAATCCGTCTCCACAGACAAGGCCAGGACTCGTTTGTACCCG-TTGATGATAGAATGGG] (Sigma-Aldrich, St. Louis, MO). The standard curves allow the assessment of the sample telomere DNA length based on the ratio of telomere DNA length to 36B4 DNA length. DNA from a short telomere cell line (HEK293) and a long telomere cell line (K562, ATCC, Manassas, VA) were used as inter-experimental plate controls.[5] The ABI ViiA 7 Real Time PCR System (Applied Biosystems, Foster City, CA) was used to run samples in triplicate. The telomere lengths measured reflect an average length across the population of leukocyte cells included in the sample.

Expanded statistical methods

Data structure

The frailty index (FI) as the main predictor variable, as well as age and other demographic variables were collected at every visit; visits within time frames shorter than 6 months were excluded in order to avoid overlapping observation periods. Absolute telomere length (aTL) as the secondary predictor variable was collected only once in a subset of patients who consented to donation of blood for research purposes.

The primary mortality endpoint was time to the composite of death or lung transplantation based on previous observations of comparable disease severity in patients that are about to decease and patients undergoing lung transplantation. We performed a pre-specified sensitivity analysis with death and lung transplantation as competing risks (i.e., once a patient was transplanted, he or she was unable to contribute a subsequent mortality event to the analysis).

We divided the observation time in intervals defined by the time points of FI and covariate assessment in order to account for repeated FI measurement per patient and for time-dependent covariates (e.g. FI, age, pulmonary function).[6] Other outcomes were assessed within the 6-month time periods after every FI assessment: 1) rate of all-cause hospitalisations, 2) rate of respiratory related hospitalisations, 3) time to hospital discharge for the patients with hospitalisations, 4) occurrence of medication adverse reaction (MAR) for the patients treated with antifibrotic or immunosuppressive medications.

Data analysis

Descriptive statistics are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]). Between group differences were analysed for statistical significance by chi-square or Fisher's exact test for categorical variables and by two-sample t-test or Wilcoxon rank sum test for continuous variables. Data were analyzed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[7]

<u>Mixed effects models</u>

We applied (generalized) linear mixed models with random intercepts for every patient since multiple FI measurements from the same patient cannot be regarded as independent from each other. The unadjusted models included FI as a fixed effect. These models were adjusted for potential

confounders of the effect of FI on adverse health outcomes. We considered confounders with either conceptual importance (age, sex) or a statistically relevant relationship to the outcome of interest ($p<0.1$). Consequently, the adjusted models included age, sex, forced vital capacity %-predicted (%FVC), diffusion capacity of the lung for carbon monoxide %-predicted (%DLCO), and a diagnosis of idiopathic pulmonary fibrosis (IPF) as fixed effects. We used the *R package lme4* for these analyses with functions lmer and glmer for linear and generalized linear mixed models, respectively.[8]
The same data analysis strategy was applied for different outcomes. The rates of all-cause and respiratory-related hospitalisations within 6 months were modeled by generalized linear mixed models with a Poisson distribution family and a log link function. The probability of MAR within 6 months from FI assessment was modeled using a generalized linear mixed model with a binomial family distribution and a logit link function (i.e. a logistic mixed model). SGRQ was modeled using linear mixed models fitted by restricted maximum likelihood (REML) with Satterthwaite's approximations for the degrees of freedom.
Model specification and standardized residuals were examined, including assessment for normality and homoscedasticity, over-dispersion, zero-inflation, and auto-correlation. The *R package DHARMa* was used for these analyses.[9]

Survival analysis

Time to death or lung transplantation and time to hospital discharge were each modeled with Cox proportional hazards regression models with intervals of time accounting for time-dependent covariates. Unadjusted models for FI and adjusted models including the above covariates were used to test the independent association of frailty with mortality. Model performance was measured using the Harrell's C-statistic. The independence between residuals and time (proportional hazards assumption) was tested using Schoenfeld residual tests.[10]
A prespecified sensitivity analysis with death (without lung transplantation) and lung transplantation as competing risks was performed by subdistribution hazard models according to Fine and Gray.[11]
The *R packages survival* and *cmprsk* were used for these analyses.[12,13]

Causal mediation analysis

A causal mediation analysis (CMA) was performed with the goal to estimate average direct effects of chronological age on adverse health outcomes and indirect effects of chronological age mediated by either biological age (aTL) or functional age (FI) (Figure S1). We performed a three-step procedure: First the *mediator models* were created by modelling the mediators separately (aTL and FI) as a function of the exposure (chronological age), second the *outcome models* for 2-year survival (logistic regression), rate of all-cause and respiratory-related hospitalisations (Poisson regression) were built, and third the two models were integrated into the *mediation model*, which estimates the strength of direct and indirect effects for an increase in chronological age by one year.[14]
To keep the models parsimonious, no additional covariates were included in the models.
Assumptions for causal mediation analysis include the absence unmeasured confounding between the mediator and the outcome, which is typically untestable. We performed sensitivity analyses in order to estimate how strong a confounder would have to be to change the conclusion of the model: Unmeasured confounding between the mediator and the outcome leads to correlation between the residuals in the *mediator* and the *outcome regression models*. We tested the potential strength of the correlation between model residuals that would cause the estimated indirect effect to change direction.[14] CMA was performed with the *R mediation* package.[15]

Table S1. Baseline characteristics of patients with CTD-ILD, unclassifiable ILD, IPF and hypersensitivity pneumonitis.

	CTD-ILD (n=227)	Unclassifiable (n=127)	IPF (n=100)	HP (n=47)
DEMOGRAPHICS				
Sex, men	53 (23%)	72 (57%)	75 (75%)	18 (38%)
Age, years	60.1 (12.7)	68.9 (10.6)	70.9 (8.0)	63.9 (10.0)
Body mass index, kg/m^2	26.3 (5.6)	29.5 (5.3)	27.9 (4.9)	30.8 (5.8)
Ever-smoker	101 (43%)	65 (51%)	62 (62%)	25 (53%)
Smoked pack-years*	10 (2.25-26.3)	19.5 (9.5-36)	72 (58.8-82.3)	18.1 (7.8-38.2)
ILD SEVERITY				
FVC, %-predicted	76.1 (21.5)	73.8 (21.4)	72.0 (17.3)	70.4 (20.6)
FEV_1, %-predicted	76.5 (22.1)	76.9 (22.1)	76.0 (17.2)	74.1 (21.2)
DLCO, %-predicted	54.0 (19.2)	56.6 (19.5)	45.1 (13.7)	53.1 (15.9)

Data are presented as mean (standard deviation), median (interquartile range), or frequency (percentage).
*in ever-smokers
Abbreviations: CTD, connective tissue disease; DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; FEV_1, forced vital capacity in one second; FVC%, forced vital capacity %-predicted; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis

Table S2. Baseline characteristics of patients with IPF and non-IPF ILDs in the full cohort and the sub-cohort with blood samples for absolute telomere length measurement available.

	Full cohort		Telomere cohort	
	IPF (n=100)	Non-IPF ILD (n=440)	IPF (n=41)	Non-IPF ILD (n=148)
Age	69.7 (8.5)	62.9 (12.6)	68.1 (8.2)	61.6 (11.9)
Sex, male	75 (74%)	157 (36%)	30 (73%)	57 (39%)
Body mass index, kg/m^2	27.9 (4.9)	27.8 (5.8)	29.0 (4.7)	27.3 (5.4)
Ever smoker	62 (62%)	210 (48%)	33 (80%)	85 (57%)
Smoked pack-years	23.5 (13-37)	15 (4-31)	20.0 (12.8-35)	12 (4-25.3)
ILD SEVERITY				
FVC, %-predicted	72.0 (17.3)	74.7 (21.5)	75.0 (17.0)	76.0 (20.3)
FEV_1, %-predicted	76.0 (17.2)	76.1 (22.1)	79.6 (17.5)	78.0 (20.3)
DLCO, %-predicted	45.1 (13.7)	54.6 (19.2)	45.3 (13.9)	54.4 (17.4)
QUALITY OF LIFE				
SGRQ, total	46.9 (23.0)	42.9 (21.8)	50.9 (21.0)	46.4 (18.6)
SGRQ, activity	63.3 (28.1)	57.2 (25.8)	57.8 (24.4)	55.3 (25.9)
SGRQ, symptom	48.5 (24.7)	48.5 (23.4)	54.5 (23.9)	46.1 (24.0)
SGRQ, impact	36.7 (23.1)	32.6 (23.1)	31.3 (17.3)	30.1 (23.1)
FRAILTY				
Frailty Index	0.167 (0.092-0.288)	0.214 (0.095-0.333)	0.146 (0.071-0.262)	0.181 (0.043-0.348)
Co-FI	0.111 (0.097-0.211)	0.158 (0.055-0.214)	0.105 (0.105-0.158)	0.105 (0.053-0.211)
I&SC-FI	0.174 (0.077-0.391)	0.261 (0.087-0.435)	0.174 (0.043-0.348)	0.217 (0.045-0.400)
Frail (FI >0.21)	39 (39%)	233 (53%)	15 (37%)	70 (47%)
Prefrail (FI 0.1-0.21)	28 (28%)	91 (21%)	10 (24%)	25 (17%)

Data are presented as mean (standard deviation), median (interquartile range), or frequency (percentage).
*in ever-smokers
Abbreviations: DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; FEV_1, forced vital capacity in one second; FVC%, forced vital capacity %-predicted; ILD, interstitial lung disease; SGRQ, St. George's Respiratory Questionnaire.

Figure S1. Directed acyclic graph

The directed acyclic graph illustrates the hypothesized mediation of the effect of chronological age on adverse health outcomes by either functional age or biological age.
Abbreviations: FI, frailty index; aTL, absolute telomere length

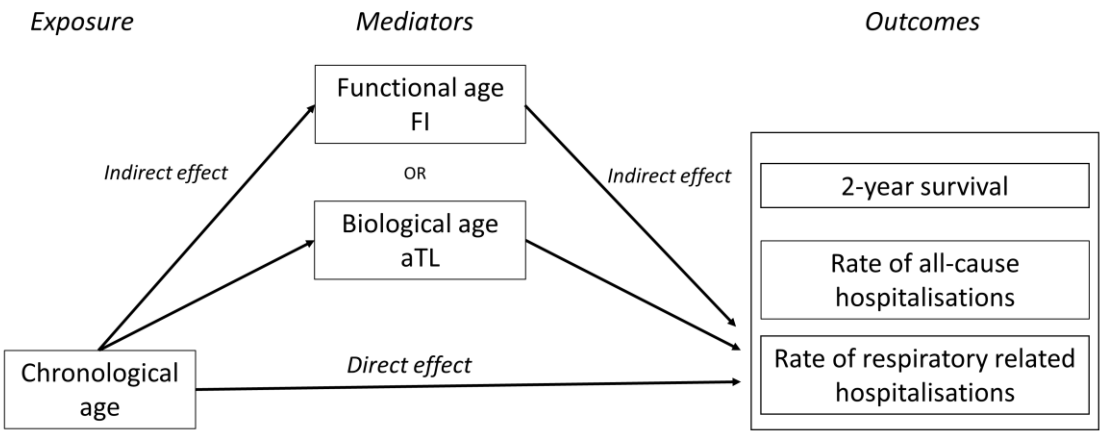
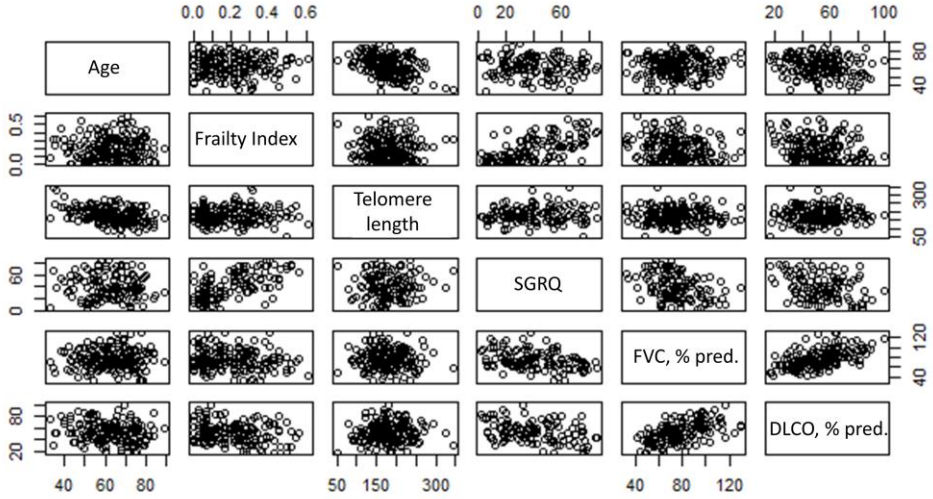


Figure S2. Pairwise scatterplots.
Scatterplots for age, Frailty Index, absolute telomere length, quality of life, and pulmonary function tests.
Abbreviations: DLCO%, diffusion capacity of the lung for carbon monoxide %-predicted; FVC%, forced vital capacity %-predicted; SGRQ, St. George's Respiratory Questionnaire.



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