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Frailty predicts outcomes in cystic fibrosis patients listed for lung transplantation

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KEYWORDS:
lung transplantation outcomes;
cystic fibrosis;
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BACKGROUND: Survival predictors are not established for cystic fibrosis (CF) patients listed for lung transplantation (LT). Using the deficit accumulation approach, we developed a CF-specific frailty index (FI) to allow risk stratification for adverse waitlist and post-LT outcomes.

METHODS: We studied adult CF patients listed for LT in the Toronto LT Program (development cohort 2005-2015) and the Swiss LT centres (validation cohort 2008-2017). Comorbidities, treatment, laboratory results and social support at listing were utilized to develop a lung disease severity index (LI deficits, d = 18), a frailty index (FI, d = 66) and a lifestyle/social vulnerability index (LSVI, d = 10). We evaluated associations of the indices with worsening waitlist status, hospital and ICU length of stay, survival and graft failure.

RESULTS: We studied 188 (Toronto cohort, 176 [94%] transplanted) and 94 (Swiss cohort, 89 [95%] transplanted) patients. The median waitlist times were 69 and 284 days, respectively. The median follow-up post-transplant was 5.3 and 4.7 years. At listing, 44.7% of patients were frail (FI $\geq$ 0.25) in the Toronto and 21.3% in the Swiss cohort. The FI was significantly associated with all studied outcomes in the Toronto cohort (FI and post-LT mortality, multivariable HR 1.74 [95%CI:1.24-2.45] per 0.1 point of the FI). In the Swiss cohort, the FI was associated with worsening waitlist status, post-LT mortality and graft failure.

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Take home message: In CF patients listed for lung transplantation in 2 independent cohorts, a frailty index constructed from routine multidisciplinary lung transplant assessments allowed risk stratification for adverse waitlist and post-transplant outcomes.

Abbreviations: AUC, area under the curve; BCC, *Burkholderia cepacia* complex; BMI, body mass index; CF, cystic fibrosis; CF-RD, CF-related diabetes; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; LAS, lung allocation score; LT, lung transplantation; NPV, negative predictive value; PPV, positive predictive value; QoL, quality of life; ROC, Receiver Operating Characteristics

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CONCLUSIONS: In CF patients listed for LT, FI risk stratification was significantly associated with wait-list and post-LT outcomes. Studying frailty in young populations with advanced disease can provide insights on how frailty and deficit accumulation impacts survival.

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Although the life expectancy of people living with cystic fibrosis (CF) has improved significantly, respiratory failure remains the main cause of mortality.[1] In selected patients with end-stage lung disease, lung transplantation (LT) provides a survival and quality of life (QoL) benefit.[2,3] Currently, no single clinical or laboratory parameter permits accurate patient risk-stratification.[4] Moreover, as the CF population ages, pulmonary and extra-pulmonary complications increase medical complexity, rendering decision-making difficult. The few predictive tools available are not CF-specific[5] and/or assess only a few disease components, some of which LT restores.[5-7]

Frailty is an age-associated state of increasing vulnerability for adverse outcomes. Of several frailty measures,[8,9] 2 predominate: the frailty phenotype[10] and the deficit accumulation/frailty index.[11,12] The phenotype evaluates 5 parameters (unintentional weight loss, exhaustion, low grip strength, slow walk speed, low physical activity) which are either self-reported or measured prospectively and assesses frailty categorically. A frailty index (FI) counts health deficits (e.g., symptoms, signs, comorbidities, disabilities and laboratory values) to derive a continuous score; higher values indicate a greater degree of frailty.[11,13] The FI is calculated as the ratio of deficits present to deficits assessed for a given individual. Estimates become more precise the greater the number of variables included in the FI.[14] Using this approach, deficits are not weighted in the FI and frailty can be conceptualized as a network in which the damage of interconnected nodes (representing deficits) makes additional damage more likely.[15]

The FI has a dose-response association with mortality[16,17] especially in older adults.[17] In younger people, its predictive role for mortality is unclear[18] likely reflecting their generally low death rate. Currently, we know little of the prevalence and impact of frailty in CF. The frailty phenotype was assessed in a small group of LT recipients with CF.[19] Improvements in frailty (evaluated with the Short Physical Performance Battery) were associated with less disability and improved QoL.[20] Although some studies have evaluated the frailty phenotype in LT candidates, no CF-specific analysis is available.[21-25] A study in 144 LT candidates (2 with CF), observed that a FI > 0.25 was associated with decreased post-LT survival.[24] In solid organ transplant candidates including 28 patients with CF, our group identified patients at risk for adverse outcomes when applying the FI.[25] Recent consensus reports have endorsed the development of frailty assessment tools as a future direction of research for transplantation studies.[26-28]

We hypothesized that the FI could integrate the multiple elements routinely assessed during CF and LT evaluation to quantify risk and that, although LT would improve pulmonary impairment, increased frailty and social/lifestyle vulnerability would negatively impact post-LT outcomes. Our aim was to develop a CF-specific FI to allow risk stratification of CF patients listed for LT and to validate this approach in an independent cohort.

Methods

Patient population

Adult CF patients listed in 2 independent cohorts, the Toronto LT Program between 2005 and 2015 and the Swiss LT centers (Zurich University Hospital and the Centre Universitaire Romand de Transplantation including Lausanne University Hospital and Geneva University Hospitals) between 2008-2017 were eligible for inclusion in this retrospective cohort study. Re-transplantation and multi-organ transplantation at study entry were exclusion criteria. The Toronto LT Program data were retrieved from its database, the Adult CF center database and clinical charts. Swiss LT centers data were retrieved from patient charts and from the Thoracic Surgery Division database of Lausanne University Hospital. All individuals had provided written informed consent for use of their data for research. The protocol was approved by the local ethics committees.

Deficits included in the 3 indices

Variables eligible for inclusion in the indices came from routine CF clinic visits and LT candidacy assessments. All parameters were associated with health status. Selection of the deficits for inclusion in the final indices (Table 1) was based on the procedure previously described by Searle et al.[14] Briefly, each deficit was present in at least 1% of subjects, was missing in <20% of participants and was expected to increase with age and/or advanced CF disease. We considered that deficits fulfilled this latter criterion if they had been reported in an earlier FI or were age-related in the general population. Deficits for which such evidence was lacking were independently assessed by 3 authors (ALS, KR, AK) who considered clinical relevance, age-association in the CF population and prevalence by age in the studied cohort. Tables S1-S4 of the supplement provide details about the application of this standard procedure for each variable. The selected deficits were categorized as lung-specific (used for the lung index − LI), extra-pulmonary (used for the FI) and associated with patients' lifestyle/social circumstances (used for the lifestyle/social vulnerability index - LSVI).[29] Lung-specific deficits were those which impacted the lung and were expected to be restored by LT. These indices

Table 1 Characteristics of Patients Included in the Analysis

Categories	Variable		Toronto cohort (N = 188 listed, N = 176 transplanted)	Swiss cohort (N = 94 listed, N = 89 transplanted)
Demographic characteristics	Age at listing, years		29.6 (17.6-63.7)	28 (18-54)
	Age at LT, years		30 (18-63)	29 (18-56)
	Time on the waitlist, days		68.5 (1-759)	284 (0-1396)
	Sex	Male	104 (55.3%)	46 (48.9%)
Characteristics at listing	FEV_1 (% predicted)		22.5 (11.4-44.6)	25.5 (12.7-78)
	6MWD (m)		432 (29-690)	450 (150-672)
	BMI (kg/m^2)		19.4 (13.5-30.3)	18.2 (13.3-27)
	CFRD		94 (50%)	49 (52.1%)
	Pancreatic insufficiency		178 (94.7%)	89 (94.7%)
	BCC or B. gladioli	Positive	37 (19.6%)	8 (8.5%)
	Support system	Suboptimal	20 (10.6%)	1 (1%)
	Urgency status[a]	Standard urgency	100 (53.2%)	89 (94.7%)
		High urgency	81 (43.1%)	5 (5.3%)
		Highest urgency	7 (3.7%)	
Follow-up	Status change on waitlist	Worse[b]	55 (29.3%)	18 (19.1%)
	Transplant status	Transplanted	176 (93.6%)	89 (94.7%)
		Died on the waitlist	12 (6.4%)	5 (5.3%)
	Re-LT during follow-up		18 (10.2%)	3 (3.2%)
	Patient status at end of follow-up	Alive	109 (58%)	69 (73.4%)
		Deceased	79 (42%)	25 (26.6%)
	Duration of follow-up after LT, years		5.3 (0.09-11.5)	4.7 (0.5-11.4)
Indices	Lung index		0.43 (0.18-0.66)	0.41 (0.12-0.75)
	Frailty index		0.25 (0.09-0.57)	0.19 (0.08-0.36)
	Lifestyle index		0.28 (0-0.9)	0.10 (0-0.70)

BCC, *B. cepacia* complex; BMI, body mass index; CFRD, CF-related diabetes; FEV_1, forced expiratory volume in 1 second; LAS, lung allocation score; LT, lung transplantation; 6MWD, 6-min walk distance.

Results are expressed as median (range) or as n (%). FEV_1 % predicted value calculated according to the recommendations of the Global Lung Function Initiative.

[a]Urgency status at listing used by the Toronto LT program.

[b]Worsening on the list refers to increased urgency status or death on the waitlist.

were first developed using the Toronto cohort and then validated in the Swiss cohort.

Coding of the deficits and creation of the indices

For coding deficits, categorical, ordinal and interval variables were mapped to the interval 0 to 1; 0 indicated absence of the deficit and 1 its full expression.[14] Each LI, FI and LSVI were calculated at listing for LT as the ratio of deficits present to the number of deficits assessed. Patients were excluded if >20% of the items for an index were missing. Clinical parameters used for the indices were standard elements of CF and LT candidacy assessment recorded routinely in the charts when present. When a variable defined by medical history (e.g. pneumothorax) was not mentioned in the charts, it was considered absent in the specific patient and a default score of 0 was assigned. Regarding laboratory values / measurements, when the result was not available this was deemed "missing."

Outcomes

We evaluated worsening status on the waitlist, post-LT mortality, graft failure (i.e., death or re-transplantation), and lengths of intensive care unit (ICU) and hospital stay after LT. Worsening status on the waitlist was defined as death on the waitlist or upgrade of patient prioritization to the highest urgency status. The Toronto LT program uses 3 levels of prioritization status: standard, high and highest urgency. The Swiss LT centers use 2 levels: standard and highest urgency.

Statistical analysis

For descriptive statistics, a cut-off of the FI≥0.25 was used to define frailty based on previous publications.[16,24] For all other analyses the FI was assessed as a continuous variable.[13] Spearman's correlation was used to assess associations between the indices. Association of each index with age and sex was evaluated with Spearman's correlation and Mann-Whitney test, respectively. The Kruskal-Wallis test was used for the association between the listing status and the indices. Post-transplant survival was summarized with Kaplan-Meier plots. Univariate and multivariable Cox proportional-hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI). The linearity and proportional hazards assumptions of the Cox proportional-hazards model were assessed graphically using Martingale and Schoenfeld residuals respectively. In the multivariable analyses (a) each index and (b) a full model with all indices was adjusted for age at listing, sex and time on the waitlist. For these analyses, each index was multiplied by 10, to facilitate interpretation of the HR (i.e. hazard for every 0.1 unit increase in the LI, FI or LSVI).

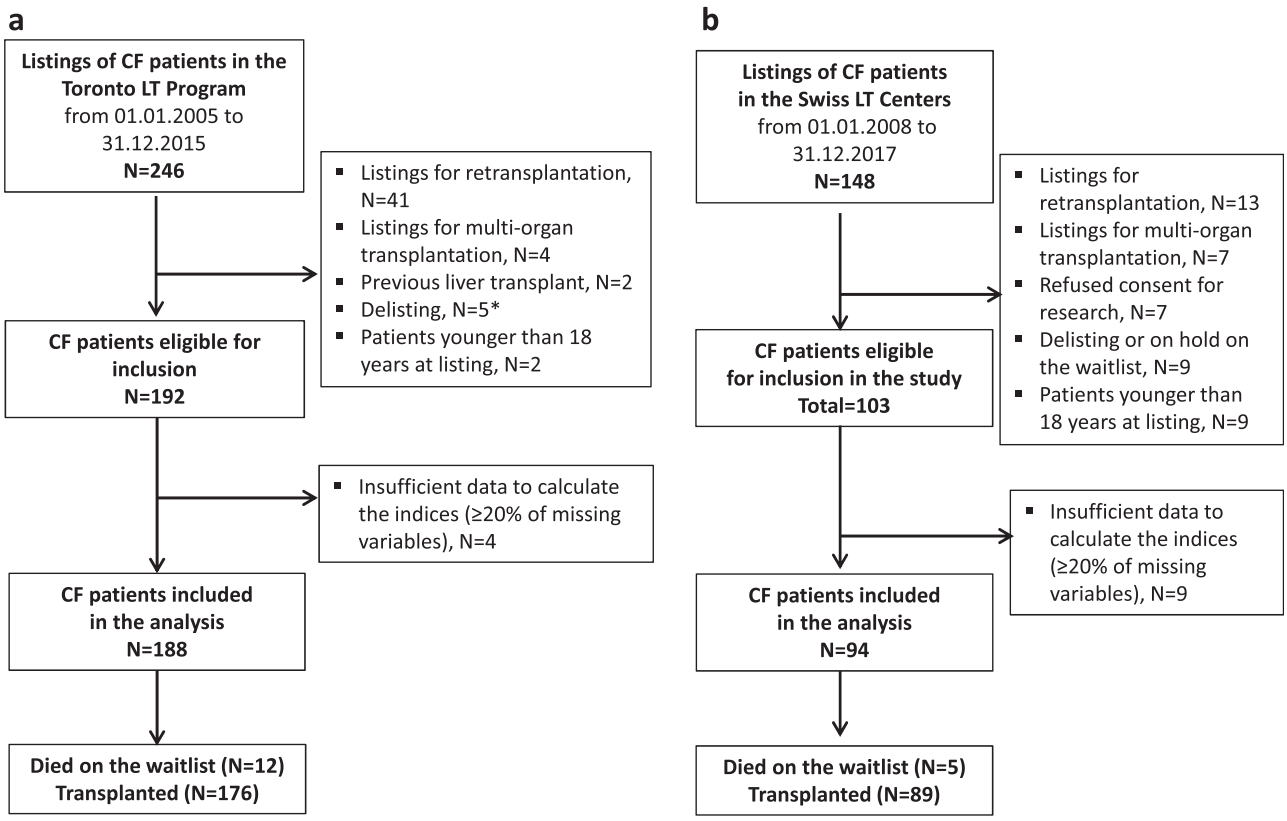

Figure 1 Flow chart diagram of the study population: (a) Toronto cohort and (b) Swiss cohort. *Two delistings concerned the same patient. Among these patients, 3 were listed at a later time-point and the last listing was included in the study. LT, lung transplantation.

In the Toronto cohort, we also performed a sensitivity analysis for post-LT mortality restricted to *Burkholderia cepacia* complex (BCC) negative patients.

We assessed overall survival for all analyses. A time-dependent ROC curve, area under the curve, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) at 6 months, 1-year, 3-years, and 5-years after LT accounting for the censored nature of the data was conducted using the timeROC package in R (version 0.4). Youden's index was considered to identify the optimal cut-point, but provided a value similar to the median. Therefore, for consistency, the median was used as the optimal cut-point for both cohorts. We report the area under the Receiver Operating Characteristic curves.

Length of ICU stay and hospital stay were modeled using linear regression models. Length of hospital stay was log-transformed to stabilize the variance. Worsening status on the waitlist was modeled as a binary outcome using logistic regression because the time-point of the status change was not available. All *p* values are 2-sided and assessed for significance at $p<0.05$. Analyses were performed using R version 3.3.0.

Results

In Toronto, 188 listed patients were included of whom 176 (93.6%) were transplanted; in the Swiss cohort 89 of 94 (94.7%) (Figure 1). The median waitlist times were 69 and 284 days, respectively. The median duration of follow-up after LT was 5.3 and 4.7 years, respectively. No patient was lost-to-follow-up. Table 1 summarizes the demographic and clinical characteristics of the studied populations. For the Toronto cohort, year 1, 3 and 5 survival was 87.9%, 77.6% and 65.6% respectively. For the Swiss cohort year 1, 3, and 5 survival was 93.2%, 88.4% and 77.9% respectively.

The LI employed 18 deficits, the FI 66 and the LSVI 10 (Table 2). In the Toronto cohort, the median (range) was 0.43 (0.18-0.66) for the LI, 0.25 (0.09-0.57) for the FI and 0.28 (0-0.9) for the LSVI. In the Swiss cohort, the median (range) was 0.41 (0.12-0.75) for the LI, 0.19 (0.08-0.36) for the FI and 0.10 (0-0.70) for the LSVI. Figure 2 shows the distribution of the 3 indices. Considering a cut-off of FI≥0.25 to diagnose frailty, 44.7% of patients were frail at listing in Toronto and 21.3% in the Swiss cohort. Associations of the indices with age, sex, urgency listing status and with each other are presented in the Figures S2-S4 and Table S5 of the Supplement.

Toronto cohort (development cohort)

The FI was significantly associated with each outcome in both the univariate and multivariable analyses (Table 3). Regarding post-LT overall survival, the FI had a HR 1.74 (95%CI:1.24-2.45) in the multivariable analysis indicating that for every 0.1 point increase in the FI, the risk for post-transplant mortality increased by 74%. The association of the FI with post-LT mortality remained significant after adjusting for the other indices and time on the waitlist (Table 4). In an analysis assessing only BCC negative patients (N = 155), the FI remained significantly associated

Table 2 Summary of Deficits Used for the Development of the Indices[a]

Lung index	1. History of thoracic intervention
	2. History of hemoptysis
	3. History of pneumothorax/pneumomediastinum
	4. History of ABPA
	5. History of asthmatic component or inhaled drug intolerance
	6. Use of oxygen
	7. Use of NIV
	8. Intubation, tracheostomy or ECMO/Novalung
	9. PaO_2 (at rest)
	10. $PaCO_2$ (at rest)
	11. $SatO_2$ at the end of the 6MWT
	12. FEV_1
	13. FVC
	14. Inhaled anticholinergic
	15. Inhaled corticosteroid
	16. Leukotriene modifier
	17. Inhaled dornase alpha
	18. Inhaled antibiotic
Frailty index (FI)	*History*
	1. Abdominal surgery
	2. Gastroesophageal reflux
	3. Other gastroesophageal disorder
	4. DIOS
	5. Clostridium or other colitis
	6. Liver disease (excl. cholelithiasis)
	7. Cholelithiasis
	8. Renal disorder (excl. nephrolithiasis)
	9. Nephrolithiasis
	10. CF-related diabetes
	11. Pancreatic status
	12. Other endocrine disease
	13. Osteopenia/osteoporosis
	14. Rheumatological disease
	15. Symptomatic sinus/nasal disease
	16. Hearing/balance disorder
	17. Arrhythmia/conduction disorder
	18. Other heart disorder
	19. Arterial hypertension
	20. Dyslipidemia
	21. Thromboembolic disorder
	22. Anemia
	23. Neurological disorder
	24. Psychiatric disorder
	25. Beta-lactam allergy
	26. Allergy to antibiotics other than beta-lactams
	27. Chronic pain
	28. Malignancy
	Treatment
	29. Nutritional support
	30. Use of systemic corticosteroids
	31. Central venous catheter
	Functional status and clinical assessment
	32. Activity status/instrumental ADLs
	33. Basic ADLs
	34. 6MWT distance
	35. BMI
	36. Systolic blood pressure
	37. Diastolic blood pressure
	38. Pulse pressure
	39. Heart rate
	40. Abnormal right ventricular function
	41. Abnormal left ventricular function
	42. RVSP
	Laboratory assessment
	43. pH
	44. WBC
	45. Neutrophils
	46. Lymphocytes
	47. PLT
	48. MCV
	49. Creatinine
	50. Sodium
	51. Potassium
	52. Total calcium
	53. Phosphorus
	54. Magnesium
	55. Total protein
	56. Albumin
	57. Alkaline phosphatase
	58. INR
	59. aPTT
	60. Mantoux or Interferon-gamma release assay
	61. MRSA
	62. Pseudomonas
	63. Other Gram-negative bacteria
	64. Aspergillus
	65. BCC/B.gladioli
	66. NTM
Lifestyle/social vulnerability index (LSVI)	1. Adherence concerns
	2. Suboptimal support system
	3. Distance of residence from the lung transplant center
	4. History of smoking (excl. cannabis)
	5. History of illicit drug use (excl. cannabis)
	6. History of marijuana use
	7. History of excessive alcohol consumption
	8. Employment
	9. Marital status
	10. Caregiver of children under 18

ABPA, allergic bronchopulmonary aspergillosis; ADLs, activities of daily living; aPTT, partial thromboplastin time; BCC, *B. cepacia* complex; BMI, body mass index; DIOS, distal intestinal obstruction syndrome; ECMO, extracorporeal membrane oxygenation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; INR, international normalized ratio; MCV, mean corpuscular volume; MRSA, methicillin resistant *S. aureus*; NIV, non-invasive ventilation; NTM, non-tuberculous mycobacteria; $PaCO_2$, arterial partial carbon dioxide pressure; PaO_2, arterial partial oxygen pressure; PLT, platelets, RVSP, right ventricular systolic pressure; SatO2, oxygen saturation; WBC, white blood cells; 6MWT, 6-minute walk test.

[a]Deficits expected to be directly restored by LT were used for the lung index, extra-pulmonary deficits were used for the FI and variables associated with patients' lifestyle/social circumstances were used for the lifestyle/social vulnerability index (LSVI).Variables were collected at listing. Details on the definition of these variables are provided in Tables S1-S3 and Figure S1 of the supplement. Variables excluded from the indices are summarized in Table S4.

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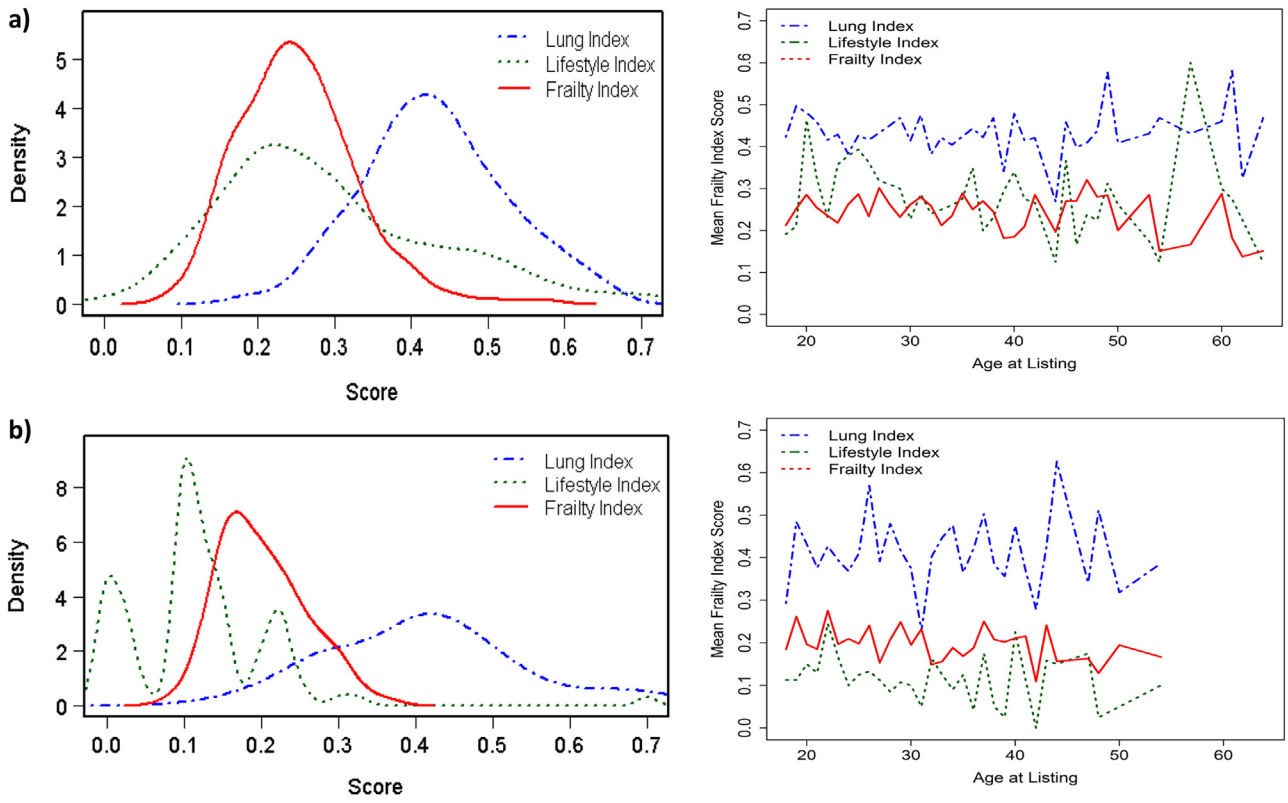


Figure 2 Distribution of the 3 indices in the studied population (a) in the Toronto cohort and (b) in the Swiss cohort.

with post-LT mortality in the univariate (HR = 1.65, 95% CI: 1.12-2.43, p = 0.012) and multivariable analysis (HR = 1.79, 95% CI: 1.18-2.71, p = 0.0058).

When the FI was dichotomized, patients with a FI≥0.25 had a worse post-LT overall survival (long-rank p-value = 0.037) (Figure 3A). Patients having FI scores ≥ 0.3 were 2.23 times more likely to die post-transplant than those with FI scores ≤0.2 (Figure 4). Using the median (0.25) as a cut-off, the sensitivity of the FI for 6-month post-LT survival was 73.2% (95% CI 50.7-95.7%) and specificity 54.1% (95% CI 46.3-62%). The positive (PPV) and negative predictive (NPV) values were 13% (95% CI 5.8-20.3%) and 95.6% (95% CI 91.3-99.8%) respectively (Figure S5 of the supplement).

The LI at listing was associated with worsening status on the waitlist whereas the LSVI had a marginally significant association with graft failure in the multivariable analysis.

Swiss cohort (validation cohort)

The FI was associated with waitlist deterioration (univariate HR 3.38 [95%CI: 1.32-8.66]) and with graft failure (multivariable HR 2.3 [95%CI: 1-5.1]). The association between post-LT mortality and the FI was significant only in the univariate analysis (Table 3). A multivariable model adjusting for all indices (Table 4), resulted in a HR 2.08 (95% CI: 0.93-4.65) between post-LT mortality and the FI.

With a categorical FI, patients with a FI>0.19 had a worse post-LT overall survival (long-rank p value = 0.032) (Figure 3B). Patients with FI scores between 0.2-0.3 were 4.3 times more likely to die post-transplant than those with FI<0.2 (p = 0.04). Interpretation for patients with a FI ≥0.3 was limited by this group's small number (n = 4). Using the median (0.19) as a cut-off, the sensitivity of the FI regarding 6-month post-LT survival was 66.7% (95% CI 13-100%) and the specificity was 52.4% (95% CI 41.6%-63.1%). The PPV and NPV were 4.7% (95% CI 0%-11%) and 97.8% (95% CI 93.6%-100%) respectively (Figure S5 of the supplement). The LI and the LSVI were associated with none of the studied outcomes.

Discussion

We evaluated the deficit accumulation approach in CF patients listed for LT. Frailty was common in this young population with advanced lung disease. A higher FI at listing was significantly associated with worsening waitlist status, post-LT mortality and graft failure in 2 independent cohorts, despite differences in the proportion of frail patients and waitlist times. The FI is the first factor described so far to allow finely-graded risk stratification for CF patients listed for LT and having the potential to quantify the multidisciplinary LT assessment across different programs.

During the adult lifespan, frailty prevalence increases with age.[11,16,30] The Canadian National Population Health Survey included more than 17,000 participants between 15 and 102 years and showed that the prevalence of frailty increases from 2% in subjects younger than 30 years to 43.7% in those aged 85+.[16] Although direct comparisons with our study may be limited by the use deficits which

Table 3 Associations of the Lung Index, the Frailty Index and the Lifestyle/Social Vulnerability Index (Per 0.1 Unit)[a] With the Outcomes in the Univariate and Multivariable Analysis (Each Index Was Adjusted for Age, Gender and Time on the Waitlist) in the Toronto and Swiss Cohorts

			Univariate			Multivariable[b]		
Outcome	Cohort	Variable	OR	95% CI	*p* value	OR	95% CI	*p* value
Worsening status on the waitlist	Toronto N = 188	Lung index	1.56	1.10-2.20	**0.012**	1.57	1.07-2.29	**0.02**
		Frailty index	2.57	1.61-4.11	**<0.001**	2.28	1.31-4.00	**0.004**
		LSVI	0.96	0.78-1.20	0.74	1.03	0.81-1.31	0.83
	Swiss	Lung index	1.19	0.8-1.78	0.39	–	–	–
	N = 94[d]	Frailty index	3.38	1.32-8.66	**0.011**	–	–	–
		LSVI	1.06	0.64-1.77	0.82	–	–	–
			Estimate	*SE*	*p value*	*Estimate*	*SE*	*p value*
Hospital length of stay[c]	Toronto N = 176	Lung index	0.06	0.05	0.25	0.06	0.05	0.27
		Frailty index	0.23	0.07	**<0.001**	0.25	0.07	**<0.001**
		LSVI	0.006	0.03	0.84	0.03	0.03	0.37
	Swiss N = 89	Lung index	0.034	0.0456	0.45	0.0327	0.046	0.48
		Frailty index	0.108	0.11	0.33	0.115	0.112	0.31
		LSVI	0.041	0.0586	0.48	0.03	0.0599	0.62
ICU length of stay[b]	Toronto N = 176	Lung index	0.096	0.07	0.18	0.09	0.07	0.19
		Frailty index	0.23	0.096	**0.016**	0.24	0.10	**0.019**
		LSVI	0.001	0.05	0.98	0.02	0.05	0.68
	Swiss N = 89	Lung index	−0.0493	0.0946	0.6	−0.0555	0.0964	0.57
		Frailty index	0.298	0.225	0.19	0.285	0.233	0.23
		LSVI	−0.0151	0.121	0.9	−0.0138	0.125	0.91
			HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Post-transplant overall mortality[d]	Toronto N = 176	Lung index	0.80	0.62-1.03	0.079	0.81	0.63-1.04	0.10
		Frailty index	1.59	1.15-2.20	**0.005**	1.74	1.24-2.45	**0.002**
		LSVI	1.16	1.01-1.34	**0.043**	1.20	1.03-1.40	**0.018**
	Swiss N = 89	Lung index	1.2	0.89-1.7	0.2	1.4	0.95-2	0.09
		Frailty index	2.4	1.1-5.1	**0.029**	2.1	0.95-4.6	0.065
		LSVI	1.1	0.75-1.7	0.53	1	0.64-1.6	0.93
Graft failure	Toronto N = 176	Lung index	0.79	0.62-1.00	**0.048**	0.80	0.63-1.02	0.077
		Frailty index	1.48	1.09-2.02	**0.012**	1.66	1.19-2.29	**0.003**
		LSVI	1.12	0.98-1.29	0.10	1.16	1.00-1.34	**0.049**
	Swiss N = 89	Lung index	1.2	0.89-1.7	0.2	1.4	0.94-2	0.099
		Frailty index	2.6	1.2-5.6	**0.018**	2.3	1-5.1	**0.039**
		LSVI	1.1	0.74-1.7	0.59	0.99	0.62-1.6	0.97

CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; LSVI, lifestyle/social vulnerability index; OR, odds ratio. Statistically significant p values ($P < 0.05$) are highlighted in bold.

[a]Each index was multiplied by 10 for these analyses to facilitate interpretation. The OR, Estimate and HR refer to a 0.1 unit increase in each index.

[b]Adjusted for age, gender and time on the waitlist (days).

[c]Each index was log-transformed to stabilize the variance. Therefore, the estimate is interpreted as a fold change. In the Toronto cohort, the FI showed an association with the length of the hospital stay and the length of ICU stay. For every single unit increase in the FI, the length of hospital stay and the length of ICU stay will be 0.24 times longer on average, after adjusting for gender, age at listing and waitlist time. The difference did not reach statistical significance in the Swiss cohort.

[d]Eighteen patients had a worsening status on the waitlist (either died or changed from standard to high urgency status). Due to the small number of events ($n = 18$), we performed only a univariate analysis. Patients with a higher frailty index were significantly more likely to experience a worsening status in the waitlist only in the Swiss cohort.

increase with advanced CF and not only with age, compared with the Canadian National Population Health Survey, our young cohort shows a frailty prevalence and median FI value corresponding to a much older population. This pronounced difference between chronological and biological age is reflected in the disproportionally high mortality risk observed in our patients, compared with the general population.[17]

To allow informed decision-making and to guide patient management and follow-up, transplant programs assess a wide range of variables.[31] In CF, several factors[4] and scores[5,6,32,33] have been studied. Mathematical models, such as the Lung Allocation Score,[5] are used to calculate the survival benefit of LT, despite their predictive value for post-LT survival not yet having been established in CF.[4] A CF-specific calculator estimated the probability of survival after LT but could not capture the transplant candidacy multidimensional assessment.[7] In the absence of established predictive tools, candidacy assessment relies on multidisciplinary expertise, providing a qualitative estimation of patients' vulnerability. Frailty can fill this gap by quantifying patient vulnerability. The FI can help with pre-transplant counselling, shared decision making and communication with the patients. Considering the poor

Table 4 Multivariable Model for Post-Transplant Overall Mortality Adjusted for all 3 Indices

	Multivariable model using the Toronto cohort		
Variable	Hazard ratio	95% CI	*p* value
Lung index	0.74	0.57-0.95	**0.020**
Frailty index	1.81	1.27-2.58	**0.001**
Lifestyle index	1.15	0.98-1.35	0.085
Age at listing	1.02	0.995-1.05	0.105
Waitlist time (per 100 days)	1.18	0.90-1.55	0.23
Sex (M vs F)	1.14	0.68-1.91	0.63
	Multivariable model using the Swiss cohort		
	Hazard Ratio	*95% CI*	*p value*
Lung index	1.37	0.95-2	0.096
Frailty index	2.08	0.93-4.65	0.075
Lifestyle index	0.93	0.6-1.43	0.73
Age at listing	0.9	0.83-0.98	**0.013**
Waitlist time (per 100 days)	0.95	0.82-1.11	0.53
Sex (M vs F)	1.12	0.42-3	0.82

In the Toronto cohort, for 2 patients with the same lung index, lifestyle index, age at listing, waitlist time and gender, the patient with the higher frailty index will be significantly more likely to die post-transplant.

Each index was multiplied by 10 for these analyses to facilitate interpretation. The HR refers to a 0.1 unit increase in each index.

Statistically significant *P* values ($P < 0.05$) are highlighted in bold.

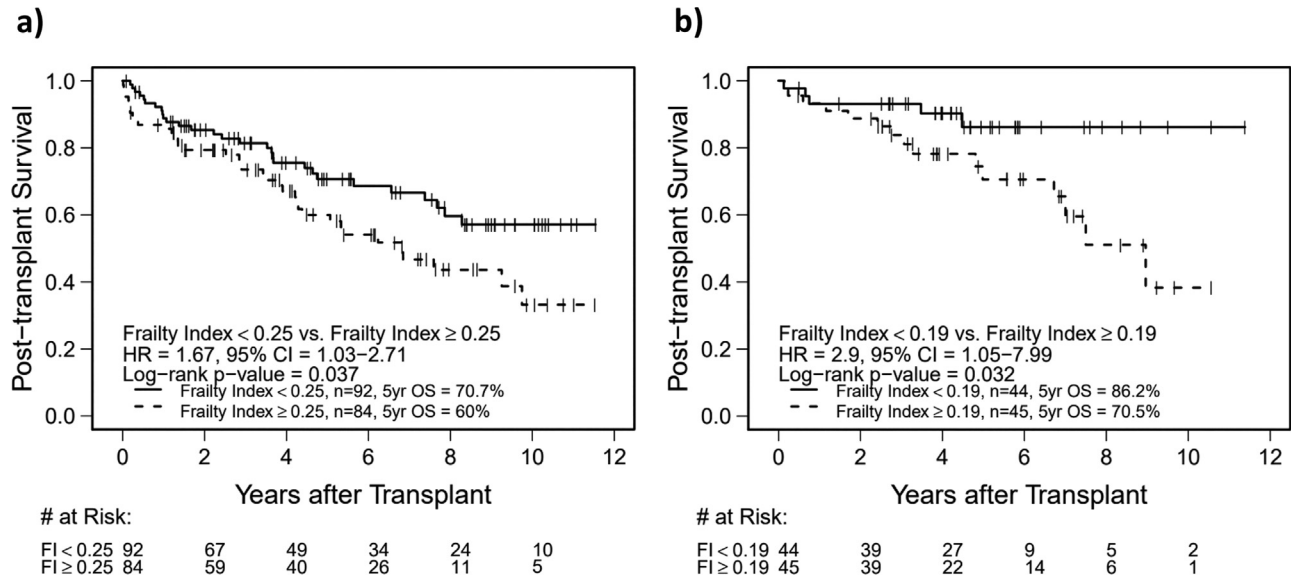
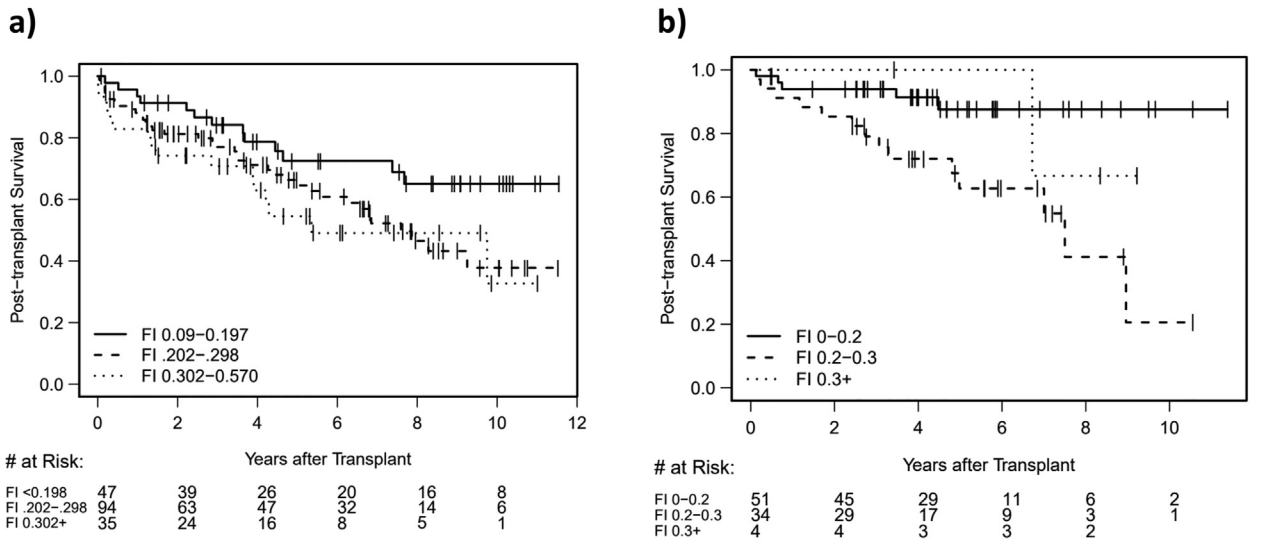


Figure 3 Kaplan-Meier plot for the frailty index (stratified according to the median value) and post-LT survival (a) in the Toronto cohort and (b) in the Swiss cohort. Footnote: For the Toronto cohort, year 1, 3, and 5 survival was 87.9%, 77.6%, and 65.6% respectively. For the Swiss cohort year 1, 3 and 5 survival was 93.2%, 88.4% and 77.9% respectively.

PPV of the FI for 6-month mortality in our study, the FI should not be used to deny listing for transplant of individuals with CF but rather can be used to identify patients with a low risk for post-transplant mortality, as indicated by the NPV of FI for 6-month mortality reaching 95.6% in the Toronto and 97.8% the Swiss cohort respectively. A systematic review identified the frailty phenotype and the deficit accumulation/frailty index as the 2 most widely used frailty instruments.[34] Here, we employed the deficit accumulation approach to capture frailty as a multidimensional risk state using existing clinical data. This approach can aid evaluation of interventions, such as LT, that are pleiotropic affecting multiple pathophysiological mechanisms.[32] Although frailty has been associated with adverse outcomes in many clinical and population settings, few studies have assessed frailty in LT, with none providing a CF-specific analysis.[35] Wilson et al reported that pre-transplant cumulative deficits frailty is highly prevalent in LT candidates, being observed in 45% of participants, and was associated with decreased post-LT survival in their single-center cohort which included only 2 CF patients.[24] Otherwise the frailty phenotype and the Short Physical Performance



FI level*	N	Number of Deaths	HR (95% CI)	p-value
<0.2	49	15	1.00	
0.2-0.3	95	39	1.82 (0.97-3.43)	0.063
>0.3	44	25	2.23 (1.07-4.64)	**0.033**

FI level*	N	Number of Deaths	HR (95% CI)	p-value
<0.2	51	5	1.00	
0.2-0.3	34	14	4.27 (1.54-11.9)	**0.0054**
>0.3	4	1	1.56 (0.18-13.5)	0.68

Figure 4 Kaplan-Meier plot according to 3 different levels of FI and post-LT overall survival (a) in the Toronto cohort and (b) in the Swiss cohort. Footnote: To facilitate interpretation of the HR, the FI index was multiplied by 10 (i.e., hazard for every 0.1 unit increase in the FI). In both cohorts, the risk of death increased with each level of the FI (overall trend test, $p = 0.028$ for the Toronto cohort and 0.04 for the Swiss cohort). In the Toronto cohort, we also tested for a statistical interaction between this 3-level categorization of the FI and both the Lung Index and the LSVI. If the interaction was significant, this would suggest that the effect of the lung Index or LSVI on mortality depended on the strata of the Frailty Index. Both interactions were found to be non-significant ($p = 0.56$ for the Lung Index, $p = 0.16$ for the LSVI).

Battery predicted delisting or death before LT[22] and early post-LT mortality.[23] In another Toronto cohort of 221 patients (48 with CF) who participated in a rehabilitation program while on the LT waiting list, the frailty phenotype did not predict post-LT outcomes but frail patients derived a significantly larger functional and QoL benefit from LT.[21] Finally, Varughese et al showed that the cumulative deficits approach can identify solid organ transplant candidates at high risk for adverse outcomes.[25] These results accord with our CF-specific study, corroborating the importance of frailty in risk-stratifying LT candidates and possibly as a response indicator for interventions considering that many deficits are dynamic may be potentially reversible.

The FI at listing was associated with all post-transplant outcomes in the Toronto cohort (development cohort). In the Swiss cohort (validation cohort), a significant association was observed with deterioration on the waitlist, post-LT mortality and graft failure. Differences regarding waitlist times (longer in the Swiss cohort) and patient characteristics (lower frailty at listing in Switzerland) may account for these discrepancies. These results indicate that the FI provides clinically relevant information even in populations with significantly different characteristics allowing risk stratification for adverse outcomes and reinforcing the generalizability of this approach in other LT programs. A worse LI was associated with worsening waitlist status in the Toronto cohort (a finding not possible to validate in the Swiss cohort due to the small number of events) but with none of the other outcomes, an expected finding considering that LT would restore pulmonary deficits. Interestingly, a higher LSVI in the Toronto cohort was associated with graft failure possibly by affecting post-LT treatment adherence and/or access to care. By dissecting the contribution of pulmonary, extrapulmonary and lifestyle/social loss of reserves, we found the FI to be an independent factor for patient risk stratification. Overall, these results indicate that a systematic, standardized evaluation of frailty but also the LI and the LSVI in CF patients listed for LT could identify high-risk patients, facilitate informed decision-making and optimize follow-up. This is especially relevant for deficits amenable to improvement (e.g., nutritional status, diabetes control, adherence, suboptimal support system).[26,36] Recognizing the impact of deficit accumulation on patient outcomes highlights the importance of early preventive strategies whenever possible.

In the general CF population, routine frailty assessment might facilitate identification of vulnerable patients and allow early interventions. So far, 1 study evaluated frailty in the general CF population, using the frailty phenotype.[19] Despite a small sample size ($n = 18$), it was significantly associated with poorer lung function and more frequent use of intravenous antibiotics.[19] The deficits included in the 3 indices for assessing LT candidates could be applied in CF more generally. Variables relevant only to LT (Table S4)

were excluded from the indices to permit later implementation in the general CF population.

Inflammaging, a term that describes chronic stimulation of the innate immune system by endogenous (e.g. microbiota, pro-inflammatory cytokines) and exogenous stimuli (e.g. diet, pathogens, pollution) is considered a risk factor for morbidity and mortality.[37,38] Although the link between frailty and inflammaging is not fully elucidated, several studies report associations between frailty and pro-inflammatory markers.[39,40] In LT, frailty has been associated with interleukin-6 and tumor necrosis factor receptor-1.[22] In CF, the vicious cycle of infection and parenchymal lung destruction, and accumulation of comorbidities with aging may accelerate inflammaging contributing to poor patient outcomes. Here, although several laboratory parameters were assessed, we could only evaluate routinely measured variables. Future studies employing biological markers in CF could offer insights into mechanisms by which early-onset frailty, rapid deficit accumulation and accelerated inflammaging impact outcomes in young adulthood. This is important given that highly efficient CFTR modulators may mitigate deficit accumulation.

This study has some limitations. First, it is retrospective, although the deficits used for the indices were standard elements of CF assessment recorded routinely and accessible prospectively. The few patients excluded for missing data demonstrate the generalizability and feasibility of our approach. Second, the large number of variables could limit the use of indices in practices without electronic medical records. Considering that LT is complex and costly, and that accurate risk stratification is essential, using electronic medical records to capture routinely recorded parameters seems warranted. Third, studies focusing on LT are inevitably associated with selection bias, as candidates with significant comorbidities may not be listed for LT. However, absolute contraindications for LT are rare in the relatively young CF population.[31] Fourth, although we included several deficits in the indices, some potentially useful items were not routinely assessed (e.g. markers of nutritional status more sensitive than BMI or parameters missing in >20% of patients). Further studies should identify sensitive markers of disease progression to include in frailty indices and assess additional patient-reported outcomes. Finally, frailty is a time-dependent covariate, obliging longitudinal assessment to provide a more dynamic picture of patient vulnerability. We calculated indices at listing to capture time-points most informative for decision-making when the CF team may still intervene to optimize pre-LT health.

In summary, CF a multisystem disease characterized by significant phenotypic variability in chronic inflammation could be a model for studying frailty in younger people. This study demonstrated the feasibility of the deficit accumulation approach in this context. The FI can quantify the multidimensional patient assessment, estimating patient vulnerability for adverse waitlist and post-LT outcomes. A standardized assessment of the degree of frailty in CF can inform decision making, identify potentially modifiable risk factors, and potentially optimize patient follow-up and relevant translational research.

Authors' contributions

AK contributed to the study design, data collection, manuscript drafting, revision and acquisition of funding. JS contributed to data analysis and revision of the manuscript. OT provided methodological and statistical advice and revised the manuscript. KR contributed to study conception, provided methodological advice and revised the manuscript for important intellectual content. CS contributed to data collection and revised the manuscript for important intellectual content. MFD contributed to data collection. CC, CB, JDA, TK, PSG, CVG and ET revised the manuscript for important intellectual content. LGS and ALS contributed to study conception, study design and revised the manuscript for important intellectual content. All authors reviewed the study findings, read and approved the final version before submission.

Disclosure statement

The authors have no conflicts of interest to disclose.

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The protocol of this project was approved by the local ethics committees (study numbers for Switzerland 2018-00367, Toronto General Hospital 16-5344, St. Michael's Hospital 16-108) and by the Swiss Transplant Cohort Study (STCS - Project No 130). Although no STCS data were used for this study, we verified that none of the patients included in the Swiss cohort had refused to participate in the STCS which would indicate refusal to use their data for research.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.07.017.

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