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Cumulative Deficits Frailty Index Predicts Outcomes for Solid Organ Transplant Candidates

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Background. Despite comprehensive multidisciplinary candidacy assessments to determine appropriateness for solid organ transplantation, limitations persist in identifying candidates at risk of adverse outcomes. Frailty measures may help inform candidacy evaluation. Our main objective was to create a solid organ transplant frailty index (FI), using the cumulative deficits model, from data routinely collected during candidacy assessments. Secondary objectives included creating a social vulnerability index (SVI) from assessment data and evaluating associations between the FI and assessment, waitlist, and posttransplant outcomes. **Methods.** In this retrospective cohort study of solid organ transplant candidates from Toronto General Hospital, cumulative deficits FI and SVI were created from data collected during candidacy evaluations for consecutive kidney, heart, liver, and lung transplant candidates. Regression modeling measured associations between the FI and transplant listing, death or removal from the transplant waitlist, and survival after waitlist placement. **Results.** For 794 patients, 40 variable FI and 10 variable SVI were created (258 lung, 222 kidney, 201 liver, and 113 heart transplant candidates). The FI correlated with assessment outcomes; patients with medical contraindications (mean FI 0.35 ± 0.10) had higher FI scores than those listed (0.29 ± 0.09), $P < 0.001$. For listed patients, adjusted for age, sex, transplant type, and SVI, higher FI was associated with an increased risk of death (pretransplant or posttransplant) or delisting (hazard ratio 1.03 per 0.01 FI score, 95% confidence interval, 1.01-1.05, $P = 0.01$). **Conclusions.** A cumulative deficits FI can be derived from routine organ transplant candidacy evaluations and may identify candidates at higher risk of adverse outcomes.

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As organ transplantation experience accrues, access to transplantation has expanded to include older and more medically complex patients.[1-3] Careful evaluation of transplant candidates is required to maximize the likely benefit from scarce donor organs[4] and minimize recipient harm. Candidates undergo a comprehensive multidisciplinary assessment to measure disease severity, determine appropriate transplant timing, optimize comorbidities and socioeconomic factors, and predict benefit or risks. As the field of transplantation progresses, evidence-based candidacy decision making is increasingly necessary. The American and Canadian Societies of Transplantation have recognized the potential improvement in candidacy evaluation by measuring frailty and noted that the ideal frailty measure for transplant is undetermined; many unanswered questions remain.[5]

Frailty is a multiply determined clinical state of increased susceptibility to physiologic stressors, leading to adverse medical outcomes.[6,7] It is associated with mortality, institutionalization, hospitalization, postoperative complications, and poor quality of life.[6,8-11] Frailty increases postoperative mortality even in low-stress procedures.[12] Despite being evaluated predominantly in elderly people, frailty is seen throughout adulthood.[13,14]

Various approaches to defining frailty have been developed.[15,16] The commonly used frailty phenotype (FP) requires at least 3 of the following characteristics: weakness, weight loss, exhaustion, slowness, and low physical activity.[6,16] Phenotypic frailty is associated with early hospital readmission in kidney transplant recipients,[17] waitlist mortality or delisting in liver and lung transplant candidates,[18,19] greater improvement in quality of life after kidney or lung transplant,[20,21] and mortality in lung and kidney recipients.[22,23] Phenotypically frail lung recipients demonstrated greater clinical benefit from transplantation than nonfrail recipients, and many became nonfrail after transplant.[20,24] However, the FP's specific testing (eg, hand dynamometry) would need to be added to a candidacy assessment while some FP criteria may be affected by symptoms of advanced organ failure (eg, weight changes due to fluid shifts in heart, liver, and kidney patients or dyspnea limiting ambulation in lung or heart patients).

The cumulative deficits model conceptualizes frailty by counting health deficits (symptoms, laboratory values, disabilities, and comorbidities) to arrive at a continuous frailty index (FI).[25-28] This comprehensive approach can encompass the physical, psychological, and social domains of function. Frailty increases with deficit accumulation over the lifespan, leading to many adverse outcomes, including mortality or institutionalization, and may be understood as biological as opposed to chronological age.[28-33] The cumulative deficits model has defined frailty across the age spectrum[13] and in many chronic conditions, including HIV patients,[34] left ventricular assist device recipients,[35] nonalcoholic steatohepatitis and alcoholic liver disease patients,[36] and lung transplant candidates.[37] For organ transplantation, this approach may complement current assessment procedures. Unlike the FP, which requires specific nonroutine tests that are unfeasible in critically ill patients, the cumulative deficits method can be implemented easily as potential deficits are already collected during candidacy evaluation, providing a more multifaceted view of frailty in the transplant population.

Typical transplant assessments evaluate social, financial, and psychological factors that may contribute to waitlist and posttransplant outcomes. Various scoring systems have been used to assess social supports and lifestyle factors such as substance abuse, adherence, and psychological health.[38-40] American transplant programs must include a "nonmedical" component to evaluation, and consensus recommendations for cardiothoracic transplant candidates illustrate the importance of these factors for adherence, survival, and quality of life.[41,42] Using a deficit accumulation approach, a social vulnerability index (SVI) can quantify these factors.[43,44]

The main objectives of this pilot study were to create and evaluate a cumulative deficits FI from the routine multidimensional assessment for solid organ transplant candidates and examine associations between frailty and transplant assessment outcomes, survival after transplant listing, and discharge disposition after transplantation. We hypothesized that frailty would correlate with adverse pretransplant and posttransplant outcomes. The contributions of social determinants were evaluated by the creation of a SVI; we hypothesized that lower social vulnerability would be protective against the effects of frailty.

MATERIALS AND METHODS

To create the cumulative deficits FI, we performed a retrospective cohort study of 815 adult patients referred for heart, kidney, liver, or lung transplant candidacy assessment at Toronto General Hospital. We included consecutive heart, liver, and lung candidates assessed between January 1, 2012, and December 31, 2013; sequential kidney transplant candidates were selected from January 1 to November 30, 2009, because of their longer transplant wait times.[45] In our program, an initial consultation was performed before starting the candidacy assessment; patients were excluded if the candidacy assessment was not initiated. Patients for multiorgan transplant evaluation were included with the primary organ group (ie, the kidney group included kidney-pancreas candidates). Retransplant candidates were also included.

Survival data were collected until January 1, 2016. The University Health Network Research Ethics Board approved this project (#15-9161-BE), waiving written consent.

The FI was developed using a standard procedure.[27] For each patient, 76 clinical variables routinely measured during candidacy evaluations and assessment and waitlist outcomes were collected from multidisciplinary team clinical transplant chart (**Table S1, SDC**, http://links.lww.com/TXD/A300). For deficit inclusion in the FI, a variable must be associated with health status and generally increase in prevalence with age without saturation (reviewed graphically and with correlation coefficients). Deficits included in the FI were chosen to encompass a range of clinical domains (Table 1).[27] Each deficit was scored as 0 (absent/normal) or 1 (present/abnormal); some deficits included partial scores (**Table S1, SDC**, http://links.lww.com/TXD/A300). For FI inclusion, we required a minimum of 85% data completeness for each deficit.

Each candidate's FI was calculated by totaling the candidate's deficits and dividing by the total available deficits scored from the patient's transplant assessment, equally weighting each deficit. Higher FI scores denote greater frailty. A patient's FI was only calculated if a minimum of 80% of deficits were scored. As some deficits in the FI were associated with the diseases requiring transplantation (eg, bilirubin in a liver candidate), a 20-variable FI (FI20) containing only deficits unrelated to any organ transplant indication was created for comparison as a sensitivity analysis.[27,31,46]

TABLE 1.

Final deficits included in the 40 variable frailty index and social vulnerability index

40 variable frailty index	
Comorbidities	**Laboratory values**
Cardiovascular disease	Hemoglobin
Respiratory/sleep-disordered breathing	*White blood cell count*
Genitourinary disease	Platelet count
Peripheral vascular disease	Estimated GFR
Cerebrovascular disease	*Sodium*
Neurologic disease	*Potassium*
Musculoskeletal disease	*Calcium*
Gastrointestinal disease	*Glucose*
Rheumatologic disease	Albumin
Hematologic disease	Alkaline phosphatase
Hepatobiliary disease	Hepatitis B surface antigen
Osteoporosis	*Cytomegalovirus serology*
Diabetes	ECG rate
Hypertension	ECG rhythm
Hyperlipidemia	**Functional status**
Malignancy history	*Basic activities of daily living*
Chronic pain	*Instrumental activities of daily living*
Hearing impairment	*Use of mobility aid*
Visual impairment	*Weight loss*
Psychiatric comorbidity	*Recent hospital admissions*
	Body mass index
Social vulnerability index	
Smoking history	Adherence
Alcohol misuse history	Finances
Recreational drug history	Relocation needs
Employment status	Distance to transplant center
Support person	English interpreter

Italicized variables were also used in the 20 variable frailty index (FI20). Bold words designate categories for the included variables.

We created a SVI using routine candidacy assessment variables[38-40,43] (Table 1 and **Table S1, SDC**, http://links.lww.com/TXD/A300). Vulnerability deficit examples include increased distance to the transplant center, absence of caregivers, and recent illicit drug use. Deficits were scored as 0 (advantageous) or 1 (disadvantageous), weighting each deficit equally. Each patient's SVI was calculated by adding their total social vulnerability deficit score and dividing by total deficits in the SVI, requiring a minimum of 80% of the candidate's deficits scored. Higher SVI denotes less favorable status. The FI, FI20, and SVI were calculated only at the time of candidacy assessment and were not updated during the waiting period.

Associations between FI and assessment and waitlist outcomes, patient hospitalization status before transplant, and discharge disposition posttransplant were measured using multivariable linear regression and multinomial logistic regression, adjusting for sex, transplant type, SVI, and age. Similarly, associations between SVI and assessment outcomes were identified with multinomial logistic regression, adjusted for sex, transplant type, and age. Variance inflation factors were used to rule out multicollinearity, and all were <1.7. Adjusted means are presented.

A composite endpoint of death on the waitlist or after transplant and delisting due to medical contraindication was used to encompass negative outcomes both before and after transplant due to the variability in waiting time to transplant among the different organ groups. Endpoints of waitlist death/delisting or death after transplant were also analyzed separately. Kaplan-Meier curves were used to assess all 3 endpoints across frailty groups, using the log-rank test to evaluate survival distribution differences. Univariable and multivariable Cox proportional hazards models were fitted to study associations between FI and survival, adjusting for age, transplant type, SVI, and posttransplant status (the latter modeled as a time-dependent covariate). Significant multicollinearity was not found in any models.

Univariable and multivariable Cox proportional hazards models for the endpoint of waitlist death or delisting for medical contraindication were repeated using the lung allocation score (LAS) for lung transplant candidates and model for end-stage liver disease (MELD) score for liver candidates.

Using the receiver operating characteristic and Youden method, the area under the curve (AUC) and a FI cutoff for waitlist death and delisting, waitlist death, posttransplant death, and the composite endpoint were calculated. Analyses were repeated with FI20.

FI and SVI were created using SPSS V24. Analysis was performed using STATA 14 and SPSS V24. For all analyses, P values of <0.05 were used as the statistical significance threshold.

RESULTS

From 76 clinical variables, a 40-deficit FI was created (Table 1). Sufficient assessment data were available to calculate FI scores for 794 patients (Figure 1). Baseline characteristics, FI and SVI of the 794 included patients are presented in Tables 2 and 3, and **Table S2, SDC**, http://links.lww.com/TXD/A300. The patients' average age was 53 years (range 18.1–74.0). FI scores ranged from 0.06 to 0.60. Frailty was not different between sexes. FI scores increased modestly with age, except in lung candidates (**Figure S1, SDC**, http://links.lww.com/TXD/A300). Liver transplant candidates were more frail than other organ groups (Table 3).

A 10 variable SVI was created (Table 1). SVI scores ranged from 0 to 0.70. Females had a lower SVI than males (Table 3). SVI scores differed between organ groups; lung transplant candidates (mean SVI 0.24 ± 0.15) had higher SVI scores than the other organ groups (liver 0.19 ± 0.12 [P < 0.001], heart 0.14 ± 0.13 [P < 0.001], kidney 0.15 ± 0.12 [P < 0.001]) (Table 3).

Following assessment, 65.2% of patients were listed for transplantation, and 45.8% were transplanted (Figure 1). Assessment outcomes varied by FI scores. Compared with candidates listed for transplant (mean FI 0.29 ± 0.09), the relative risk ratio (RR) for rejection from waitlisting for those with medical contraindications (mean FI 0.35 ± 0.10) was 1.08 per 0.01 increase in FI score (95% confidence interval [CI] 1.05-1.11, P < 0.001) and 1.05 for a 0.01 FI score rise (95% CI 1.02-1.09, P = 0.003) for those that died during assessment (mean FI 0.35 ± 0.09). Likewise, patients who were too well for transplant listing (mean FI 0.24 ± 0.07) had lower FI scores than those listed for transplant (mean FI 0.29 ± 0.09, RR 0.94 per 0.01 FI score decline, 95% CI 0.91-0.97, P < 0.001 [Table 4 and **Figure S2, SDC**, http://links.lww.com/TXD/A300]). In all organ groups, patients with medical contraindications were frailer than

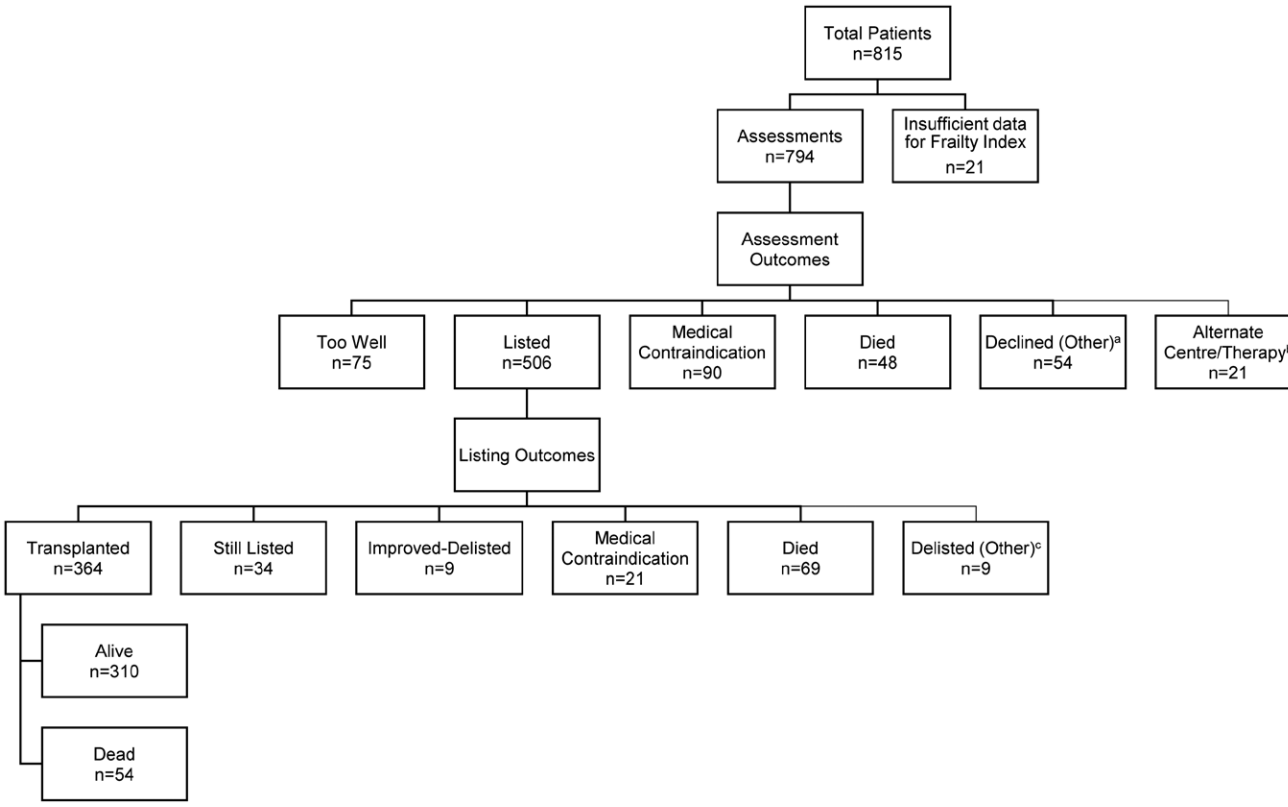

FIGURE 1. Flow diagram summarizing transplant consultation, assessment and listing outcomes, and posttransplant survival. [a]Declined (Other) includes patients declined for transplant because of financial and psychosocial reasons or those that decided to withdraw from transplant process. [b]Alternate center/therapy includes patients that have transferred to another transplant center or pursued alternate medical or surgical therapy. [c]Delisted (Other) includes patients that were removed from the waitlist because of patient preference, non-adherence, or transferred to another transplant center.

TABLE 2.

Baseline characteristics of the study population

	Full cohort	Heart[a]	Kidney	Liver	Lung
Subjects	794	113	222	201	258
Mean age	52.8 ± 12.6	50.6 ± 13.1	49.8 ± 12.9	55.7 ± 10.1	54.1 ± 12.9
Male (%)	509 (64)	88 (78)	138 (62)	136 (67)	147 (57)
Listed	506	48	156	140	162
Transplanted	364	32	116	96	120
Died on waitlist	69	4	10	19	36
Died posttransplant	54	5	7	14	28
Retransplants	44	0	30	5	9
Living donor	87	0	64	23	0
Median time between assessment and transplant excluding LD (d)	294 IQR (135–609)	220.5 IQR (81.5–397.5)	1231 IQR (657–1749)	170 IQR (82–373)	270.5 IQR (153–491)
Median time between assessment and transplant for LD (d)			480 IQR (270–832)	146 IQR (98–186)	
Median waitlist time (d)	142.0 IQR (42–464)	181.5 IQR (67.5–690)	400.0 IQR (46–1306.5)	98.5 IQR (38–265.5)	125.5 IQR (41–261)

[a]Twenty seven heart transplant candidates had left ventricular assist devices.
IQR, interquartile range; LD, living donor.

those listed for transplantation (**Table S3, SDC**, http://links.lww.com/TXD/A300).

The SVI varied between assessment outcomes. Listed candidates (mean SVI 0.18 ± 0.13) had lower SVI scores than patients declined for financial and social reasons or due to patient preference (mean SVI 0.23 ± 0.16, RR 1.04 per 0.01 SVI score increase, 95% CI 1.02-1.06, P = 0.001).

The correlation between FI and hospitalization status at the time of transplant lacked statistical significance (RR 1.03 per 0.01 FI score rise, 95% CI 0.99-1.07, P = 0.10). Of 364 transplanted patients, 306 (84%) were discharged home and 36 (10%) to a rehabilitation facility; 19 patients (5%) died during their transplant hospitalization. Three patients were discharged to another hospital with uncertain dispositions.

TABLE 3.

Frailty and social vulnerability indices of the study population

	Patients	Mean age	Mean FI	Mean FI20	Mean SVI
Total	794	52.8 ± 12.6	0.29 ± 0.10	0.25 ± 0.11	0.18 ± 0.14
Sex[a]					
Male	509 (64%)	53.0 ± 12.7	0.29 ± 0.10	0.25 ± 0.11	0.20 ± 0.14
Female	285 (36%)	52.4 ± 12.3	0.29 ± 0.10	0.26 ± 0.11	0.17 ± 0.13
Transplant type[b]					
Heart	113 (14%)	50.6 ± 13.1	0.29 ± 0.11	0.23 ± 0.10	0.14 ± 0.13
Kidney	222 (28%)	49.8 ± 12.9	0.27 ± 0.09	0.21 ± 0.11	0.15 ± 0.12
Liver	201 (25%)	55.7 ± 10.1	0.34 ± 0.09	0.29 ± 0.11	0.19 ± 0.12
Lung	258 (32%)	54.1 ± 12.9	0.28 ± 0.09	0.27 ± 0.11	0.24 ± 0.15

[a]Difference in mean SVI by sex is statistically significant ($P = 0.001$).
[b]Difference in mean SVI, mean FI, and mean FI20 by transplant type is statistically significant ($P < 0.001$).
FI, 40 deficit frailty index; FI20, 20 deficit frailty index; SVI, social vulnerability index.

Based on FI at assessment, there is a 7% increased risk of discharge to an inpatient rehabilitation facility with a 0.01 FI score rise (RR 1.07, 95% CI 1.02-1.12, $P = 0.01$) (**Table S4, SDC**, http://links.lww.com/TXD/A300).

Using FI20 instead of the 40-item FI, similar results for the above analyses were obtained (Table 3, **Tables S3 and S4, SDC**, http://links.lww.com/TXD/A300). With fewer deficits, the entire cohort had lower frailty scores with FI20 than FI. Regardless, frailty did not differ by sex; the liver (mean FI20 0.29 ± 0.11) and lung (0.27 ± 0.11) groups were frailer than the heart and kidney candidate groups (Table 3). Compared with listed candidates (mean FI20 0.24 ± 0.11), those with a medical contraindication (0.30 ± 0.13) had a 5% greater risk of rejection from waitlisting for each 0.01 increase in FI20 (RR 1.05, 95% CI 1.02-1.07, $P < 0.001$) (Table 4 and **Table S3, SDC**, http://links.lww.com/TXD/A300).

Kaplan-Meier analysis (Figure 2A) illustrated that greater frailty was associated with a higher risk of delisting for a medical contraindication and dying on the transplant waitlist or after transplant (the composite endpoint). The degree of frailty also separately correlated with death/delisting on the transplant waitlist and death after transplant (Figure 2B and C).

Univariable Cox proportional hazards models demonstrated that FI scores and age were associated with both an increased risk of the composite endpoint and the individual component outcomes of death/delisting from transplant waitlist and death after transplant (Table 5). Higher SVI scores correlated with greater risk for the composite endpoint (hazard ratio [HR] 1.02 per 0.01 SVI score rise, 95% CI 1.01-1.03, $P = 0.01$) and death after transplant (HR 1.03 per 0.01 unit SVI increase, 95% CI 1.01-1.05, $P = 0.003$).

In the multivariable analysis, higher FI scores were associated with an increased risk of the composite endpoint (HR 1.03 per 0.01 unit increase in FI, 95% CI 1.01-1.05, $P = 0.01$) and death/delisting from medical contraindication on transplant waitlist (HR 1.05 per 0.01 FI score increase, 95% CI 1.02-1.07, $P = 0.001$), adjusted for age, sex, transplant type, SVI, and posttransplant status (for composite endpoint) (Table 5). For illustration, the relative hazard of the composite endpoint is 3-fold greater for a person with an FI score of 0.50 compared to the mean FI of 0.12 in the 10% least frail waitlisted candidates.

The AUC using the receiver operating characteristic for the composite endpoint (waitlist death/delisting and posttransplant death) was 0.64. A FI score cutoff of 0.27 was calculated, based on risk of the composite endpoint; however, the FI score cutoff of 0.36 for waitlist death/delisting had better specificity of 82% (**Table S5, SDC**, http://links.lww.com/TXD/A300). FI and FI20 had similar AUC for waitlist death and composite outcomes (**Table S5, SDC**, http://links.lww.com/TXD/A300).

In univariable analysis, higher LAS in lung candidates were associated with an increased risk of the waitlist death or delisting (HR 1.15 per 1 unit increase in LAS, 95% CI 1.09-1.21, $P < 0.001$); the FI functioned similarly (HR 1.12 per 0.01 unit increase in FI, 95% CI 1.06-1.21, $P < 0.001$). After adjusting for the LAS, the association between FI and waitlist death/delisting remained significant (**Table S6, SDC**, http://links.lww.com/TXD/A300). Contrastingly, FI and MELD scores did not correlate with higher risk of the waitlist death/delisting in the univariable and multivariable analysis (**Table S6, SDC**, http://links.lww.com/TXD/A300).

TABLE 4.

Comparison of the effect of frailty on assessment and listing outcomes

	FI[a]		FI20[a]		SVI[b]	
	Relative risk ratio (95% CI)	*P*	Relative risk ratio (95% CI)	*P*	Relative risk ratio (95% CI)	*P*
Assessment outcomes						
Listed	Ref		Ref		Ref	
Too well	0.94 (0.91-0.97)	<0.001	0.96 (0.93-0.98)	0.002	1.01 (0.99-1.02)	0.60
Medical contraindication	1.08 (1.05-1.11)	<0.001	1.05 (1.02-1.07)	<0.001	1.02 (1.00-1.04)	0.04
Dead	1.05 (1.02-1.09)	0.003	1.04 (1.01-1.07)	0.003	1.03 (1.01-1.06)	0.005
Listing outcomes						
Transplanted	Ref		Ref		Ref	
Delisted-improved	0.97 (0.90-1.04)	0.43	0.99 (0.93-1.05)	0.69	1.01 (0.95-1.07)	0.85
On waitlist	1.00 (0.96-1.05)	0.98	1.01 (0.97-1.05)	0.59	1.01 (0.98-1.05)	0.41
Delisted-medical contraindication	0.99 (0.94-1.05)	0.79	1.00 (0.95-1.04)	0.87	1.01 (0.97-1.05)	0.57
Died on waitlist	1.08 (1.05-1.12)	<0.001	1.05 (1.02-1.08)	0.001	0.99 (0.97-1.01)	0.33

[a]These analyses were adjusted for age, sex, transplant type, and SVI.
[b]This analysis was adjusted for age, sex, and transplant type.
FI, 40 variable frailty index; FI20, 20 variable frailty index; SVI, social vulnerability index.

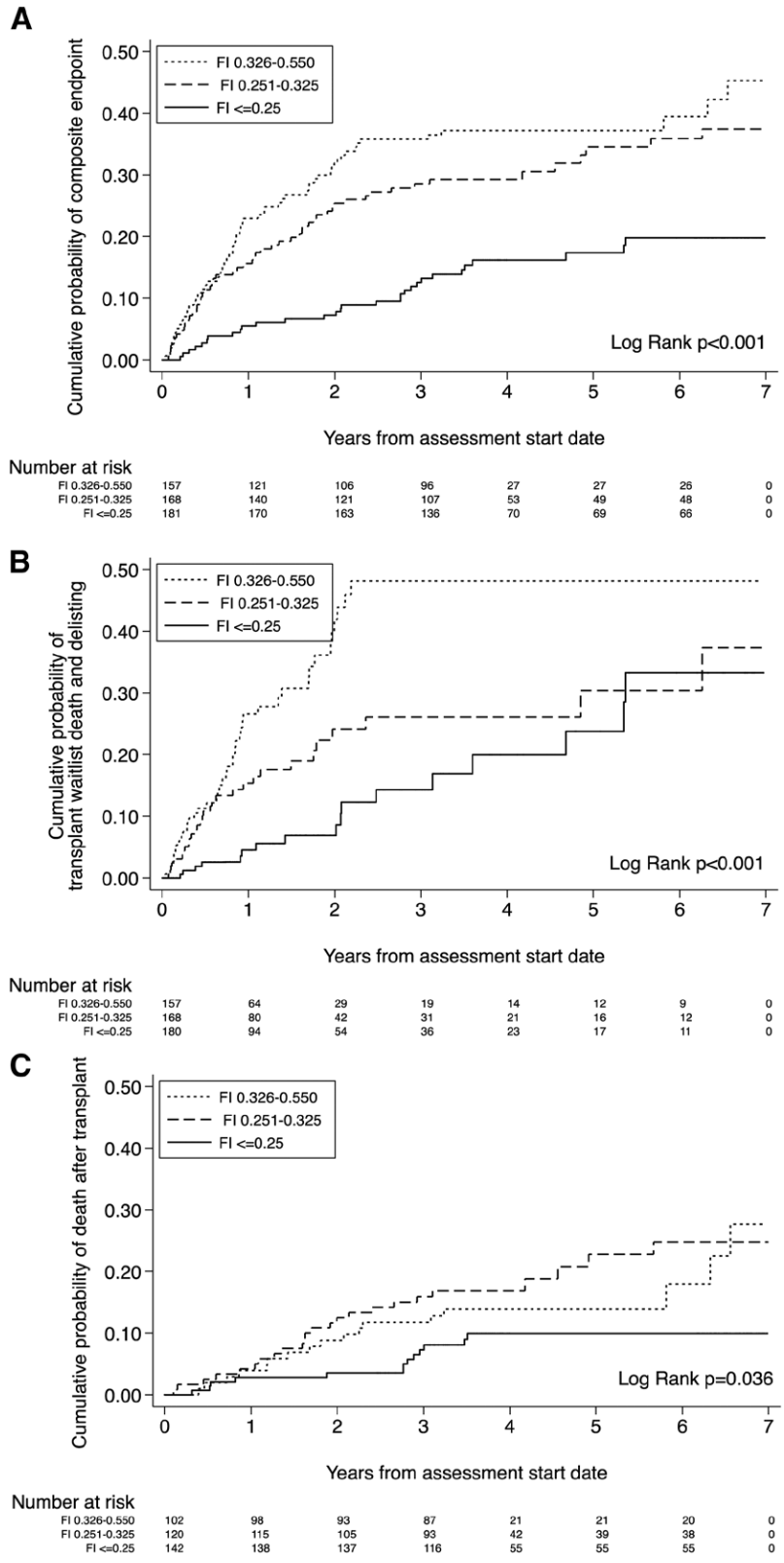

FIGURE 2. Kaplan-Meier curves of frailty effect on death or delisting from the transplant waitlist, death after transplant, and a composite combined endpoint. A, Kaplan-Meier curve of the composite endpoint of death after transplant or on waitlist and delisting for medical contraindication, showing increased frailty is associated with increased probability of death or delisting. B, Kaplan-Meier curve of transplant waitlist death or delisting due to medical contraindication. Patients censored at date of death, delisting, transplant, or censor date. With increased frailty, increased likelihood of being removed from transplant waitlist. C, Kaplan-Meier curve of death after transplantation. Two higher frailty groups have decreased survival.

TABLE 5.

Univariable and multivariable Cox proportional hazard models for transplant waitlist death/delisting, posttransplant death, and the composite endpoint, respectively

	Composite endpoint: death/delisting on transplant waitlist and death posttransplant				Endpoint: death and delisting due to medical contraindication while on transplant waitlist				Endpoint: death after transplant			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Risk factors												
FI	1.05 (1.03-1.07)	<0.001	1.03 (1.01-1.05)	0.01	1.07 (1.04-1.09)	<0.001	1.05 (1.02-1.07)	0.001	1.03 (1.00-1.06)	0.04	1.03 (1.00-1.06)	0.09
Age	1.03 (1.02-1.05)	<0.001	1.01 (1.00-1.03)	0.08	1.03 (1.01-1.05)	0.002	1.01 (1.00-1.03)	0.32	1.03 (1.01-1.06)	0.01	1.02 (0.99-1.04)	0.13
SVI	1.02 (1.01-1.03)	0.01	1.00 (0.99-1.02)	0.57	1.01 (0.99-1.03)	0.26	0.99 (0.98-1.01)	0.27	1.03 (1.01-1.05)	0.003	1.01 (0.99-1.03)	0.31
Sex (female vs male)	1.10 (0.79-1.54)	0.56	1.06 (0.75-1.50)	0.73	1.35 (0.89-2.05)	0.16	1.30 (0.84-2.03)	0.27	0.76 (0.42-1.36)	0.35	0.62 (0.34-1.14)	0.12
Transplant type												
Liver vs lung	0.80 (0.55-1.16)	0.24	0.51 (0.35-0.76)	0.001	1.16 (0.73-1.84)	0.52	0.85 (0.51-1.43)	0.54	0.52 (0.27-0.99)	0.05	0.41 (0.20-0.83)	0.01
Heart vs lung	0.56 (0.30-1.07)	0.08	0.46 (0.23-0.90)	0.02	0.51 (0.22-1.21)	0.13	0.53 (0.21-1.32)	0.18	0.75 (0.29-1.96)	0.56	0.83 (0.29-2.36)	0.72
Kidney vs lung	0.08 (0.04-0.16)	<0.001	0.04 (0.02-0.10)	<0.001	0.04 (0.02-0.12)	<0.001	0.05 (0.02-0.12)	<0.001	0.04 (0.01-0.16)	<0.001	0.04 (0.01-0.18)	<0.001
Transplant (yes vs no)	0.15 (0.11-0.21)	<0.001	0.09 (0.07-0.14)	<0.001								

CI, confidence interval; FI, 40 variable frailty index; SVI, social vulnerability index.

DISCUSSION

In this pilot study, we have developed the first cumulative deficits FI for solid organ transplant candidates using only elements from the comprehensive transplant candidacy evaluation. This exploratory study illustrates that the degree of frailty is measurable from a routine transplant assessment without additional testing and that frailty is a predictor of pretransplant and posttransplant outcomes.

Considering that disease progression affects physical conditioning, performance of activities of daily living, and function of other organ systems, transplant candidates should be frailer than the average person. We found that transplant candidates are strikingly more frail than the typical Canadian population.[13] Our Canadian transplant population's mean FI of 0.29 is similar to the mean FI of people aged 85–90 years in the Canadian National Population Health Survey despite our patients' mean age of 53.[13] Nonetheless, this study demonstrates a range of frailty in transplant candidates with only 1/3 of patients having frailty indices <0.25.

In this introductory work, the FI correlated with adverse outcomes even before transplantation. Patients with a higher FI were more likely to have medical contraindications or to die during the assessment period compared to candidates accepted for listing. This ability to quantify the degree of frailty from routinely collected data lends rigor to the currently more subjective determination of frailty during candidacy assessment. The high degree of frailty observed in our cohort suggests that the "eye-ball" test does not exclude all frail patients from transplant listing. Current practices of using disease-specific risk prediction factors with age-based clinical impressions of robustness may exclude patients with potential transplant benefit or fail to identify patients with imminent death risk; the FI may help recognize these specific patient groups. Based on the modest AUC for prediction of adverse outcomes, the FI alone is inadequate to exclude candidates from transplant listing.

Without measuring frailty explicitly, candidacy assessment methods may miss opportunities to identify and intervene on frail patients. The cumulative deficits approach mimics the stereotypical evaluation as a large amount of data, including medical history, investigations, and functional assessments, are assessed to determine candidacy; however, the FI integrates this subjective process into an objective frailty measurement. As patients with higher FI scores were more likely to die on the waitlist or to require rehabilitation admission after transplant, identification of frailty during assessment could improve transplant outcomes if frailty can be effectively alleviated. Mitigation of frailty is an active area of inquiry on several fronts.[47-49]

Chronologic age remains a relative contraindication to transplantation in many programs. Frailty is a powerful predictor of transplant outcomes independent of age. In our multivariable model, every 0.01 increase in FI is associated with a 3% higher risk of delisting or death in the follow-up period; age did not independently predict mortality. At any age, a range of FI scores was observed, illustrating that age itself is neither a sensitive nor a specific marker of risk in the transplant population.

Literature using the cumulative deficits frailty approach in transplant and end-stage organ dysfunction is growing. A deficit accumulation index showed a mean frailty score of 0.27 for stage 5 chronic kidney disease.[50] The cumulative deficits FI measuring frailty before left ventricular assist device insertion for destination therapy noted the same mean frailty score (0.29) as our study; typically, destination therapy is considered for heart failure patients with contraindications to heart transplantation.[35] Using adaptations of Rockwood's 2005 FI, frail patients with nonalcoholic hepatosteatosis had an increased risk of delisting, whereas frailty before lung transplant was associated with decreased survival after transplant.[36,37] These studies support our cumulative deficits approach although refinement with serial measurements and careful outcome measurement are needed.

Although frailty measures specific to individual organ groups may be informative, the transplant frailty literature

predominantly uses the FP to define frailty in all organ groups. Other models, such as sarcopenia and short physical performance battery, have also been used.[18,19,51-57] Our study's FI for transplant candidates demonstrates similar findings to studies using other frailty models in the transplant population. In this study's deficit accumulation model, higher frailty is associated with increased risk of waitlist death/delisting and posttransplant death. Likewise, phenotypic frailty in heart, kidney, liver, and lung transplant candidates correlates with waitlist mortality[18,19,53,56] and with mortality after transplant in kidney and lung transplant recipients.[22,23] In kidney, liver, and lung candidates, the short physical performance battery also correlates with waitlist delisting/death and posttransplant mortality.[19,22,55,58] By encompassing additional domains important for candidacy assessment, deficit accumulation may provide a more holistic frailty measure for transplant than other measures while eliminating the need for specialized testing to measure frailty.

The creation of the FI in this exploratory study was constrained by the differences between the transplant assessments for each organ group; more liver disease associated deficits (eg, alkaline phosphatase) were common to all organ groups and, therefore, included in the final index. As a sensitivity analysis, we created a "clean" 20-deficit FI, removing deficits associated with heart, kidney, liver, and lung disease severity. FI20 outcomes were similar to FI; liver transplant candidates were frailer than the others in both indices, supporting 40-item FI validity. Cumulative deficit frailty indices better characterize frailty when they include at least 30-40 potential deficits.[27,31,46] More deficits make smaller incremental change to frailty, whereas fewer deficits create instability in the FI.

Social vulnerability was associated with assessment outcomes. The SVI variables can heavily weigh into transplant candidacy. Some transplant centers exclude patients due to the absence of a support person, whereas patients may decline transplantation due to financial constraints and relocation requirements. Although higher SVI was a mortality risk factor in the univariable analysis, SVI did not correlate significantly with survival in the multivariable analysis and may not be as important a determinant of transplant outcome as frailty. The SVI may have greater importance in other populations as the Canadian healthcare system may partially mitigate some challenging social determinants of health. Future comparison of SVI with validated transplant psychosocial measures, serial measurements, and in larger cohorts is required.

This pilot study has some limitations. In this study, the deficits were assessed retrospectively; some potential deficits, such as hypercholesterolemia, were excluded from this FI if they were frequently undocumented. Prospective collection of deficits may improve the FI's predictive validity. This study also included a few multiorgan transplant candidates who may be frailer due to multisystem disease. The limited number of patients and deaths in each organ-specific group reduced our power to identify organ-specific associations. There may be referral bias due to nonreferral of potential transplant patients perceived as frail. Our study cohort did not include referred patients that were not formally assessed for candidacy, excluding patients deemed too fit or too frail for transplant consideration. We also were only able to evaluate frailty at the time of candidacy assessment and not immediately before transplant.

Extrapolating from other populations,[13,31,59] frailer patients at transplant assessment have greater risk of developing more deficits while waiting for transplant, leading to worse outcomes. Serial FI measurements may describe how frailty changes from assessment to listing to receiving the transplant and whether transplantation itself changes frailty and may help identify the influence of waitlist and posttransplant interventions, such as nutrition and physical rehabilitation, in improving frailty or attenuating negative outcomes associated with frailty.[60-64] Although the physical frailty by FP is better defined in the transplant literature, the FI potentially provides a better multidimensional view of frailty. Comparisons of FI to other frailty measures, such as the FP, Clinical Frailty Scale, and Liver FI, are required to help determine the optimal role for each measure.[27,65-67]

Validation of our findings in larger single and multiorgan transplant cohorts and at different centers is underway. Although we anticipate that this study's findings are generalizable, a predominantly male Canadian population was used; transplant candidacy eligibility criteria, such as age, and recipient and donor management may have changed since our cohort as well. Social determinants of health may affect populations with other healthcare systems differently, altering the importance of the SVI and possibly even FI. Also, studying this FI's predictive value for posttransplant survival with organ-specific disease severity measures may define the role of the FI in evaluating transplant candidates and recipients. With validation cohorts, the frailty and quality of life relationship should be investigated, especially because transplantation's dual aim is to improve quality of life and life expectancy.

The cumulative deficits FI from this pilot study is a novel method to measure frailty in the solid organ transplant population, using data typically collected during the candidacy assessment. The FI's associations with assessment and listing outcomes as well as posttransplant and waitlist mortality reveal its potential utility in determining transplant candidacy, organ allocation priority, and interventions to improve transplant outcomes.

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