Prevalence and impact of frailty assessed using standard geriatrics tools in older adults with blood cancers

Clark DuMontier,[1-3] Angel M. Cronin,[3] Tammy T. Hshieh,[2-4] Ameya Sanyal,[3] Lee Mozessohn,[5] Maya M. Abdallah,[6] Daniel J. DeAngelo,[3] Nikhil C. Munshi,[1,3] Richard M. Stone,[3] Robert J. Soiffer,[3] Jane A. Driver[1,2#] and Gregory A. Abel[3,7#]

[1]Veteran Affairs Boston Healthcare System, New England GRECC, Boston, MA, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Marcus Institute for Aging Research at Hebrew SeniorLife, Boston, MA, USA; [5]Sunnybrook Odette Cancer Centre, Toronto, Ontario, Canada; [6]Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA and [7]Center for Bioethics, Harvard Medical School, Boston, MA, USA

[#]*JAD and GAA contributed equally as senior authors.*

Correspondence: C. DuMontier
cdumontier@bwh.harvard.edu

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Abstract

Geriatric assessment is recommended for older adults undergoing cancer treatment, but the best frailty assessment tools for blood cancers have still not been identified. We conducted a prospective cohort study of three gold standard approaches: the cumulative deficit index, phenotypic frailty, and 4-meter gait speed. From February 2015 to January 2025, a research assistant approached patients aged ≥73 years attending new consultations for leukemia, lymphoma, and multiple myeloma. A total of 1,011 patients underwent frailty assessment with a median age of 78 years (interquartile range [IQR]: 76-82 years) and a median follow-up among survivors of 43 months (IQR: 18-74 months). For example, when classified by phenotypic frailty, 11% were frail, 59% pre-frail, and 30% robust; using this tool, frail patients lived 24 months compared to 92 months among robust patients. While frailty classification varied across measures, all three tools were associated with mortality in a dose-dependent manner, independent of age and sex (cumulative deficit index: ref=robust; pre-frail HR 1.86 [95%CI: 1.54, 2.26]; frail HR 2.42 [1.85, 3.17]; phenotypic frailty: ref=robust; pre-frail HR 1.88 [1.50, 2.37], frail HR 3.01 [2.22, 4.07]); gait speed: ref=≥0.8 m/s; 0.6 to <0.8 m/s HR 1.44 [1.18, 1.76], <0.6 m/s HR 2.06 [1.61, 2.63]). Associations were similar when analyzed by disease clinic; cumulative deficit further stratified risk in patients assessed by phenotypic frailty and gait speed. Our findings provide a new benchmark on frailty and its impact on survival in older adults with blood cancers, with care delivery implications for operationalization in clinical practice and research.

Introduction

Older adults constitute the growing majority of patients with hematologic malignancies.[1-3] A formal assessment of frailty (a state of reduced physiologic reserve that leaves one vulnerable to stressors[4]) is now recommended via geriatric assessment for all older (aged 65+ years) adults with cancer who are receiving systemic therapy.[5] Various frailty assessment tools have been adapted for use in older patients with leukemia, lymphoma, and multiple myeloma;[6-10] however, data are lacking regarding well-established tools that have been extensively applied and validated in geriatrics and aging research. Many still question whether the value of these assessment tools justifies the time needed for use in busy oncology practices,[11,12] the majority of which do not have access to a geriatrician. To address these gaps in evidence, hematologic oncologists and geriatricians founded the Older Adult Hematologic Malignancy (OHM) Program at Dana-Farber Cancer Institute in 2015.
Frailty is a latent construct that cannot be directly observed or measured, but two approaches to its operationalization have prevailed: the Rockwood deficit accumulation model (referred to as "cumulative deficit index")[13] and the Fried phenotype model (referred to as "phenotypic frailty").[14] The cumulative deficit index posits that frailty arises from the collective effect of multiple aging-related health deficits across organ systems. It quantifies the geriatric assessment of medical comorbidities, cognition, and function into one measure; the more deficits present within and across these domains, the lower one's physiological reserve, thus reflecting a loss of 'redundancy' and ability to maintain homeostasis when facing stress.

In contrast, phenotypic frailty posits that frailty is a syndrome defined by five features: unintentional weight loss, exhaustion, weakness, slowness, and low physical activity.[14] These features aggregate when age-related cellular dysfunction contributes to dysregulated energy metabolism and muscle loss (sarcopenia). Finally, gait speed, the measure used to define one of the five features of phenotypic frailty (slowness), has emerged as a brief but powerful summary measure of frailty that can be more easily incorporated into clinical workflows than full frailty assessments.[15] All three frailty assessment tools have their advantages and disadvantages, but to date, no comparative analysis has been carried out in a population of older adults with blood cancers.

We report on the Older Adult Hematologic Malignancy (OHM) Program's comprehensive analysis of these three summary measures of frailty, the cumulative deficit index, phenotypic frailty, and gait speed. We further analyzed the impact of each frailty assessment measure on survival, with follow-up data spanning the decade since our Program's inception. Our analyses provide data regarding frailty on a population-level, assessed using gold standard tools from geriatrics and gerontology, to guide implementation in clinical practice and decision making on a patient-level, where evaluation of cancer-specific and aging-related drivers of frailty need to be identified and targeted for intervention.

Methods

Study design and population

This is a prospective cohort study with enrollment from February 3rd, 2015, to January 16th, 2025. We included patients who attended a new consultation visit at Dana-Farber Cancer Institute in the leukemia, lymphoma, or multiple myeloma clinics, were aged 75 years and older, and underwent a frailty assessment with our research assistant. During the COVID-19 pandemic, we started to offer virtual assessments.[16] In October 2020, we lowered the age limit from 75 to 73 to expand enrollment while not overwhelming our research staff, based on review of patient volume across our blood cancer clinics. We excluded patients without any follow-up in our health system after their initial frailty assessment and patients who did not have the minimal necessary data for all three frailty measures to be calculated. The study was approved by the Dana-Farber Harvard Cancer Center Office for the Protection of Human Research Subjects (protocol #14-515).

Frailty measures and survival

The OHM Program frailty assessment includes 42 patient-reported and objective performance items spanning the health domains of functional status (ADL/IADL), mobility and muscle strength, nutrition, cognition, comorbidity, and social support. Deficit accumulation frailty, phenotypic frailty, and 4-meter gait speed were derived from this frailty assessment; full details are included in the *Online Supplementary Methods* and *Online Supplementary Tables S1-S3*. We leveraged a large, health system–based cohort in which survival could be reliably ascertained across clinics and hospitals. We have previously shown that our virtual assessments classify frailty in a similar way to the in-person assessments, although they may, to some degree, select a lower proportion of frail patients.[16] Virtual assessments are both safe and feasible, including the completion of objective performance measures such as cognitive assessments and 4-meter gait speed (completed over videoconference using a 4-meter strip of ribbon sent to patients' homes).

Statistical analysis

Demographic and clinical variables were descriptively summarized using frequency and percentages for categorical variables, and mean, standard deviation, median, interquartile range (IQR), and range for continuous variables. Overall survival probabilities were estimated using the Kaplan-Meier method with differences evaluated by the log rank test. Cox proportional hazards regression models were fit for four models in primary analyses: 1) age + sex (base model); 2) age + sex + cumulative deficit index; 3) age + sex + phenotypic frailty; and 4) age + sex + gait speed. Frailty is a multidimensional domain that arises among patients with cancer due to underlying pre-cancer fitness, impact of the cancer, and toxicity of cancer treatment. These factors are difficult to distinguish from each other, since cancer-related factors may be collinear and/or intermediate variables. For this reason, given the heterogeneity of cancer types in our cohort and because our primary interest was to estimate the association between frailty and mortality without adjustment of these factors, we did not adjust for specific markers of risk or aggressiveness pertaining to individual blood cancers (e.g., the International Prognostic Index for non-Hodgkin lymphoma). To estimate these associations with consideration of these factors, analyses were repeated by disease clinic (leukemia, lymphoma, and myeloma), followed by further adjustment of treatment intensity as a covariate to the base model. Secondary analyses considered the single items of frailty for associations with survival. We also explored whether the cumulative deficit frailty index further risk stratified patients classified as pre-frail by phenotypic frailty criteria or patients in the middle category of gait speed (≥0.6 to <0.8 m/s). The proportional hazards assumptions of the models were assessed by inspection of Schoenfeld and Martingale residuals. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17] Statistical analyses were performed using R version 4.4.1 with statistical significance defined by a two-sided *P* value <0.05.

Results

Baseline characteristics and prevalence of frailty

Our final analytic cohort included 1,011 patients (Figure 1). Median age was 78 years (IQR: 76-82 years) and 36% were female (Table 1). Patients with lymphoma represented the largest disease clinic subgroup (N=410, 41%), followed by leukemia (N=230, 23%), and multiple myeloma (N=189, 19%). When classified by the cumulative deficit index, 10% of the overall cohort was frail, 33% pre-frail, and 57% robust. When classified by phenotypic frailty, 11% were frail, 59% pre-frail, and 30% robust. The most prevalent phenotype criteria were weakness (53%), weight loss (32%), and slowness (20%). For gait speed, 15% of patients walked <0.6 m/s, 30% walked 0.6 to <0.8 m/s, and 55% walked ≥0.8 m/s. A Sankey diagram that illustrates the degree to which the cumulative deficit index reclassified patients first categorized by phenotypic frailty and gait speed is shown in Figure 2 (distribution of patients in *Online Supplementary Table S4*). The prevalence of single-item frailty measures is also presented in Table 1.

Association between frailty and survival

A total of 502 patients (50%) died in the overall cohort, with a median follow-up among survivors of 43 months (IQR: 18-74 months). Overall survival declined significantly across levels of each frailty measure (Figure 3, log rank *P*<0.001 for all measures). Patients identified as frail by the cumulative deficit frailty index had a median survival of 26 months *versus* 75 months for robust patients, compared to 24 months in patients identified as frail by phenotypic frailty *versus* 92 months for robust patients (*Online Supplementary Table S5*). Patients in the slowest gait speed category (<0.6 m/s) had a median survival of 25 months

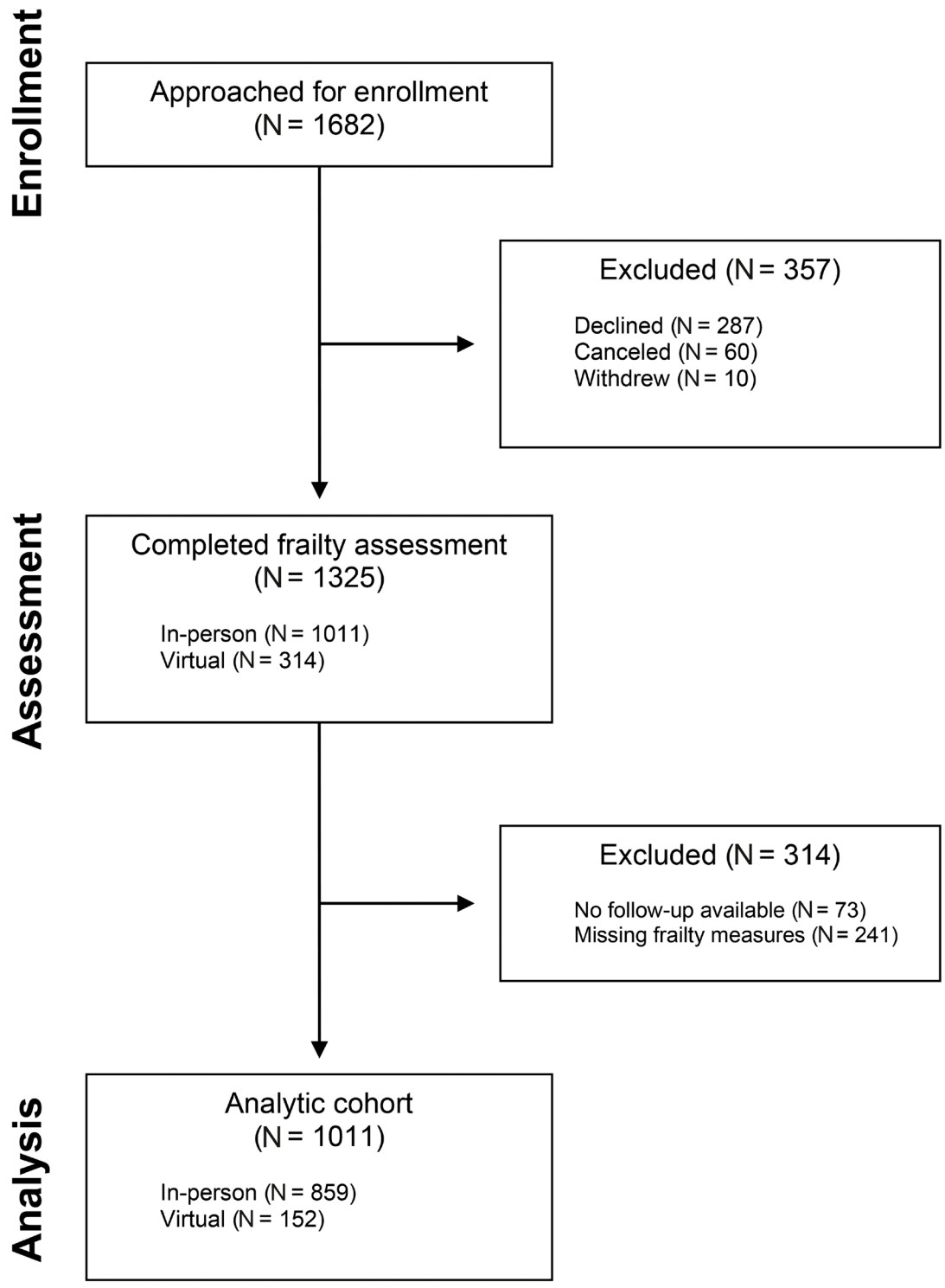


Figure 1. Flow diagram showing enrollment into study cohort.

Table 1. Demographics and clinical characteristics for the study cohort, overall and by disease clinic.

Characteristics	Overall N=1,011	Lymphoma N=410	Leukemia N=230	Myeloma N=189	Other N=182
Age at frailty assessment, years					
Mean (SD)	79.2 (4.1)	79.5 (4.2)	79.4 (4.0)	78.8 (3.9)	78.9 (4.2)
Median (Q1, Q3)	78 (76, 82)	78 (76, 82)	79 (76, 82)	78 (76, 81)	78 (76, 81)
Min - Max	73-95	73-95	73-92	73-95	73-91
Age at frailty assessment, years, N (%)					
<75	55 (5)	18 (4)	14 (6)	7 (4)	16 (9)
75-79	555 (55)	222 (54)	115 (50)	119 (63)	99 (54)
80-84	286 (28)	118 (29)	76 (33)	45 (24)	47 (26)
85+	115 (11)	52 (13)	25 (11)	18 (10)	20 (11)
Sex, N (%)					
Female	363 (36)	153 (37)	74 (32)	71 (38)	65 (36)
Male	648 (64)	257 (63)	156 (6)	118 (62)	117 (64)
Patient-reported ECOG PS,* N (%)					
0-1	902 (90)	375 (92)	198 (86)	162 (86)	167 (93)
2	67 (7)	24 (6)	22 (10)	12 (6)	9 (5)
3	34 (3)	7 (2)	9 (4)	14 (7)	4 (2)
4	3 (0)	2 (0)	0 (0)	1 (1)	0 (0)
Intensity of systemic therapy,** N (%)					
Supportive care	337 (41)	190 (46)	110 (48)	37 (20)	-
Lower intensity	191 (23)	67 (16)	90 (39)	34 (18)	-
Higher intensity	301 (36)	153 (37)	30 (13)	118 (62)	-
Gait speed, m/s					
Mean (SD)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.2)
Median (Q1, Q3)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)
Min-Max	0.0-3.7	0.0-1.8	0.0-3.7	0.0-1.6	0.0-1.5
Usual gait speed, m/s, N (%)					
≥0.8	552 (55)	228 (56)	125 (54)	97 (51)	102 (56)
0.6 to <0.8	308 (30)	121 (30)	77 (33)	51 (27)	59 (32)
<0.6	151 (15)	61 (15)	28 (12)	41 (22)	21 (12)
Cumulative deficit index, N (%)					
Robust	575 (57)	243 (59)	111 (48)	106 (56)	115 (63)
Pre-frail	338 (33)	138 (34)	94 (41)	56 (30)	50 (27)
Frail	98 (10)	29 (7)	25 (11)	27 (14)	17 (9)
Phenotypic frailty, N (%)					
Robust	305 (30)	123 (30)	56 (24)	60 (32)	66 (36)
Pre-frail	594 (59)	251 (61)	147 (64)	98 (52)	98 (54)
Frail	112 (11)	36 (9)	27 (12)	31 (16)	18 (10)
Unintentional weight loss	319 (32)	124 (30)	83 (36)	67 (35)	45 (25)
Self-reported exhaustion	111 (11)	33 (8)	30 (13)	28 (15)	20 (11)
Low energy expenditure	33 (3)	9 (2)	8 (3)	11 (6)	5 (3)
Slow gait speed	199 (20)	87 (21)	37 (16)	45 (24)	30 (16)
Weak grip strength	533 (53)	217 (53)	137 (60)	88 (47)	91 (50)
During the last week, on how many days did you walk outside? N (%)					
≥3 days	892 (88)	361 (88)	204 (89)	165 (87)	162 (89)
<3 days	119 (12)	49 (12)	26 (11)	24 (13)	20 (11)
Was the patient able to explain presentation to DFCI? N (%)					
Without help	985 (97)	402 (98)	222 (97)	183 (97)	178 (98)
With help or unable	26 (3)	8 (2)	8 (3)	6 (3)	4 (2)
Was the patient dependent on the assistance of others to complete the assessment? N (%)					
Without help	910 (90)	373 (91)	206 (90)	169 (89)	162 (89)
With help or unable	101 (10)	37 (9)	24 (10)	20 (11)	20 (11)

*Patient-reported Eastern Cooperative Oncology Group performance status (ECOG PS) was unknown for 5 patients in total (lymphoma, N=2; leukemia, N=1; myeloma, N=0; other, N=2). **Among patients with lymphoma, leukemia, or multiple myeloma. DFCI: Dana-Farber Cancer Institute; N: number; SD: standard deviation.

versus 73 months for patients in the highest gait speed category (≥0.8 m/s). In Cox proportional hazards regression models adjusted for age and sex, each frailty assessment measure was significantly associated with mortality in a dose-dependent manner (Table 2).

Compared to robust patients, patients identified as frail by the cumulative deficit frailty index had a 2.4 times higher hazard of death (hazard ratio [HR]: 2.42; 95% confidence interval [CI]: 1.85, 3.17) and patients identified as frail by phenotypic frailty had a three times higher hazard of death (HR: 3.01; 95%CI: 2.22, 4.07). Compared to patients in the fastest gait speed category, patients with the slowest gait speed had a two times higher hazard of death (HR: 2.06; 95%CI: 1.61, 2.63) and each 0.1 m/s decline in gait speed was associated with a 10% higher risk death (HR: 1.10; 95%CI: 1.07, 1.14). The single items of frailty were associated with higher mortality, although the association was not significant for the item measuring the need of assistance to complete the full frailty assessment (Table 2).

The cumulative deficit index further stratified survival in patients in the pre-frail phenotype category (Figure 4A) and patients in the intermediate gait speed category (0.6 to <0.8 m/s) (Figure 4B). Separate Cox regression models adjusting for age and sex showed that among pre-frail patients classified by phenotypic frailty, patients classified as pre-frail or frail by cumulative deficit index had higher mortality (HR: 2.33; 95%CI: 1.81, 2.99) compared to patients classified as robust by the cumulative deficit index (HR: 1.51; 95%CI: 1.16, 1.96) (Table 2). Among patients in the intermediate gait speed category, patients classified as pre-frail or frail by cumulative deficit index had higher mortality (HR: 1.92; 95%CI: 1.52, 2.43) compared to patients classified as robust by the cumulative deficit index (HR: 1.04; 95%CI: 0.79, 1.37) (Table 2).

Repeating Cox regression models by disease clinic subgroups (further adjusting for treatment intensity in addition to age and sex), the associations of each frailty measure with mortality were largely similar compared to associations in the overall cohort, although the strengths of the association varied (Table 3). Associations did not meaningfully change regardless of whether treatment intensity was controlled for in our models (*Online Supplementary Table S6*). In general, point estimates of HR for each frailty measure were higher in patients with lymphoma as compared to patients with leukemia and multiple myeloma. Among the single-item frailty measures, there was no significant association between the need for assistance to complete

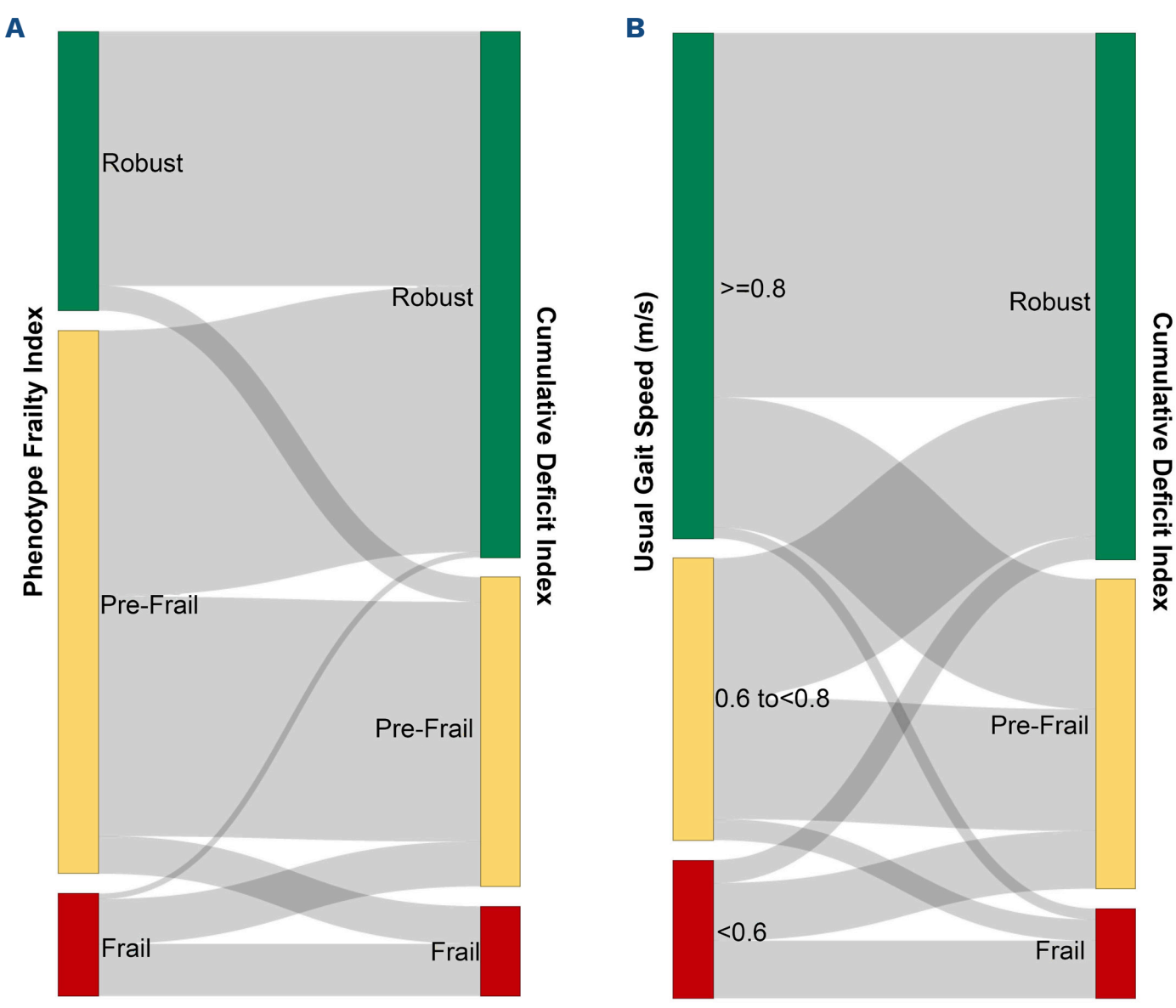


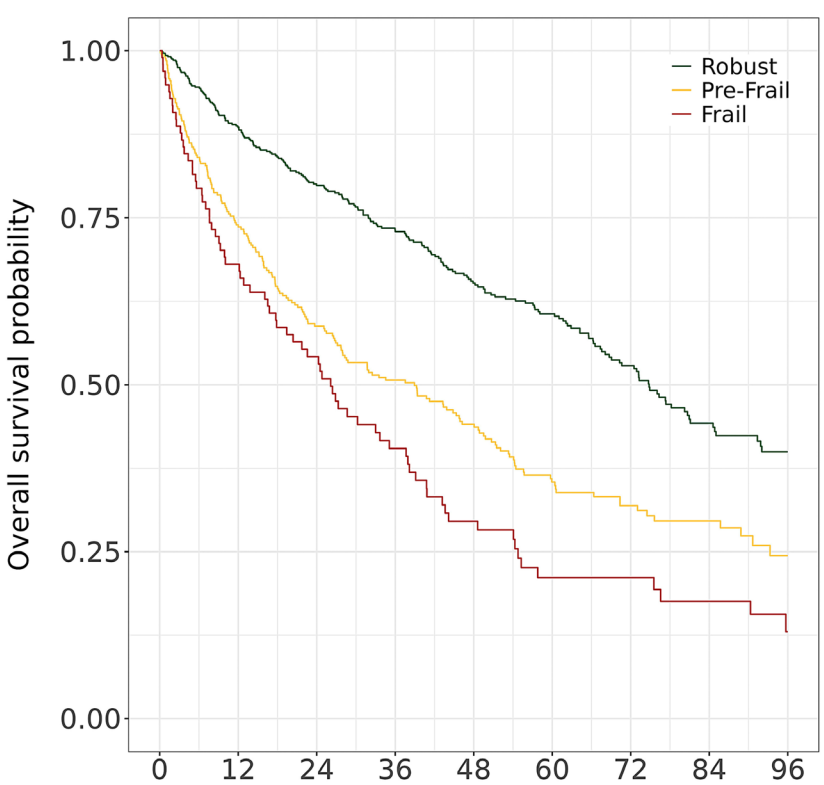
Figure 2. Sankey diagrams showing the degree to which the full 42-item cumulative deficit frailty measure reclassifies frailty in patients assessed by other tools. (A) Patients originally classified by phenotypic frailty. (B) Patients originally classified by gait speed.

the assessment and mortality among lymphoma patients, and there was no significant association between walking outside <3 days per week and mortality among multiple myeloma patients. The number of patients unable to independently explain their presentation to Dana-Farber was too small to analyze within disease subgroups.

Discussion

In this large cohort of older adults with blood cancers and long-term follow-up, pre-frail and frail states were common as measured with gold standard frailty assessment tools that are well-established in geriatrics but

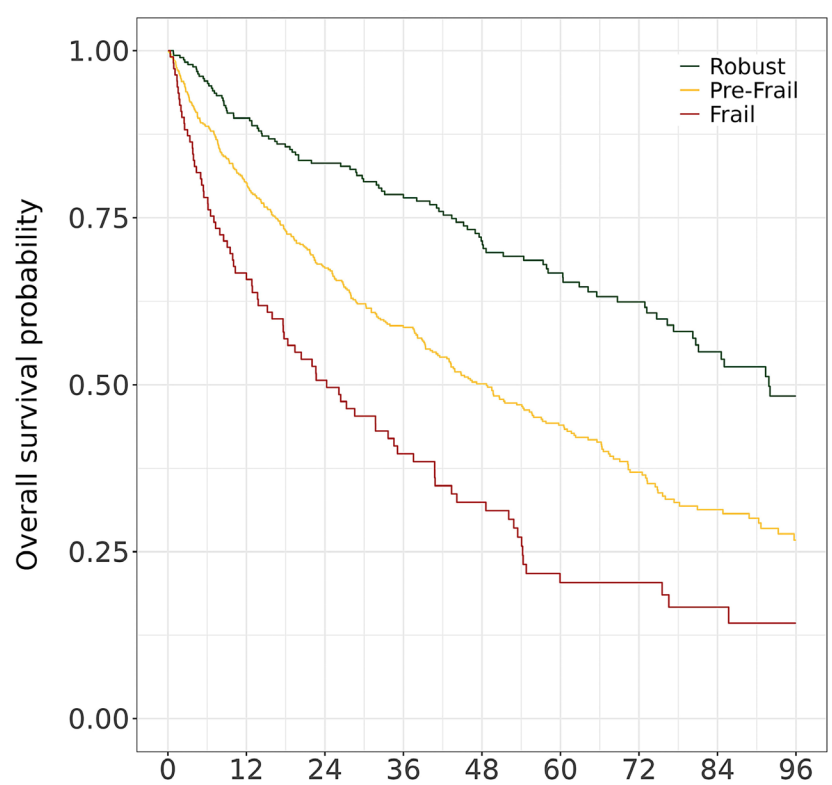
A



At Risk

Robust	575	447	359	284	222	178	121	73	40
Pre-Frail	338	224	163	130	101	69	45	31	14
Frail	98	65	49	34	24	14	12	9	5

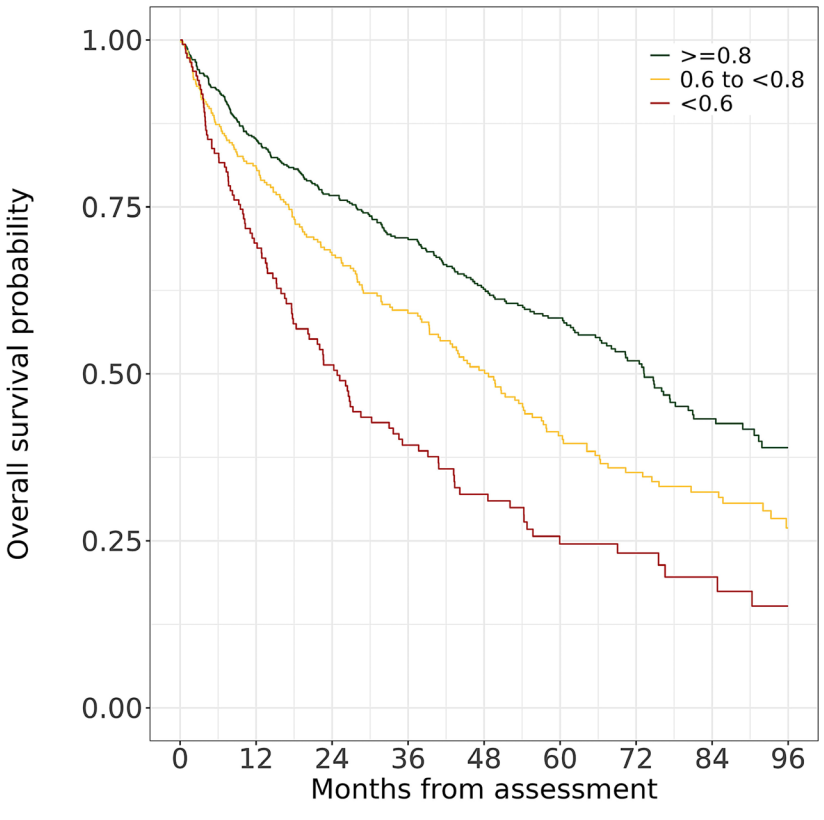
B



At Risk

Robust	305	235	189	158	125	100	78	51	27
Pre-Frail	594	432	334	256	196	146	88	54	28
Frail	112	69	48	34	26	15	12	8	4

C



At Risk

>=0.8	552	414	333	269	212	168	110	64	34
0.6 to <0.8	308	228	172	133	102	72	53	39	19
<0.6	151	94	66	46	33	21	15	10	6

Figure 3. Kaplan-Meier estimates of overall survival, stratified by increasing severity of each frailty measure. (A) Overall survival probability with frailty classified by the cumulative deficit index. (B) Overall survival probability with frailty classified by phenotypic frailty. (C) Overall survival probability with frailty classified by usual gait speed.

understudied in hematologic malignancies. The cumulative deficit index and phenotypic frailty both showed a dose-response relationship with survival, independently of age and sex in the overall cohort, and independently of age, sex, and treatment intensity in disease subgroups of leukemia, lymphoma, and multiple myeloma. Gait speed showed similar associations with survival when compared to more time-intensive frailty assessments, and single-item questions also showed promise. With these geriatric frailty assessments, our findings provide a new benchmark on frailty prevalence and its impact in older adults with blood cancers, with implications for operationalization of frailty assessment in clinical practice and research.

With over 1,000 older patients with blood cancers assessed over ten years, our data contribute a definitive and novel analysis of the prevalence of frailty in this population and a unique assessment of the comparative utility of the three tools used. Phenotypic frailty has been prospectively measured and found to be predictive of survival in smaller disease-specific cohorts of AML[18] and high-risk MDS,[19] as well as in transplant patients.[20] Phenotypic frailty has not been directly studied in lymphoma or multiple myeloma, although a fully patient-reported version has been adapted from health-related quality of life questionnaires.[21] The cumulative deficit frailty index has been assessed and associated with survival and other clinical outcomes in acute myeloid leukemia,[22] myelodysplastic syndromes,[23] lymphoma,[24] and multiple myeloma.[25] Geriatric assessment domains and simplified versions have been found to be predictive in smaller cohorts of blood cancer subtypes,[26-30] but frailty as a singular construct has been less studied. Briefer frailty tools have been adapted from gold standard

Table 2. Cox proportional hazards models for risk of mortality in older adults with blood cancers.

Frailty measure	Overall Cohort N=1,011	
	HR*	95% CI
Cumulative deficit index		
Robust	-	-
Pre-frail	1.86	1.54, 2.26
Frail	2.42	1.85, 3.17
Phenotypic frailty		
Robust	-	-
Pre-frail	1.88	1.50, 2.37
Frail	3.01	2.22, 4.07
Phenotypic frailty + cumulative deficit indices		
Phenotype (robust)	-	-
Phenotype (pre-frail) + cumulative (robust)	1.51	1.16, 1.96
Phenotype (pre-frail) + cumulative (pre-frail or frail)	2.33	1.81, 2.99
Phenotype (frail)	3.05	2.25, 4.13
Usual gait speed, m/s		
≥0.8	-	-
0.6 to <0.8	1.44	1.18, 1.76
<0.6	2.06	1.61, 2.63
Usual gait speed + cumulative deficit index		
Gait speed (≥0.8)	-	-
Gait speed (0.6 to <0.8) + cumulative (robust)	1.04	0.79, 1.37
Gait speed (0.6 to <0.8) + cumulative (pre-frail or frail)	1.92	1.52, 2.43
Gait speed (<0.6)	2.08	1.63, 2.66
Usual gait speed per 0.1 m/s decrease	1.10	1.07, 1.14
During the last week, on how many days did you walk outside?		
≥3 days	-	-
<3 days	1.35	1.05, 1.74
Was the patient able to explain presentation to DFCI?		
Without help	-	-
With help or unable	2.07	1.33, 3.22
Was the patient dependent on the assistance of others to complete the assessment?		
Without help	-	-
With help or unable	1.24	0.95, 1.61

*Hazard ratios (HR) for each variable in the table are from separate models with adjustment for age and sex. CI: confidence interval; DFCI: Dana-Farber Cancer Institute; N: number.

assessments for use within subtypes of blood cancers.[7,8] Many of these, such as the International Myeloma Working Group Frailty Score (IMWG-FS),[7] have been gaining traction in their respective fields, with increasing evidence to show that they routinely outperform historical performance status and age alone in identifying vulnerable patients at risk of treatment toxicity and inferior survival. Recent evidence in multiple myeloma suggests that cancer treatment guided by the International Myeloma Working Group frailty score (IMWG-FS) leads to improved survival compared to standard oncology care.[31] While this prior work has provided invaluable insights, our study offers unique strengths. We analyzed frailty in a significantly older population with a median age close to 80 years, capturing patients under-represented in clinical trials and even real-world studies. We administered objective performance tests (gait speed, grip strength, and the clock draw) alongside patient-reported measures and preserved the objective performance tests even in our virtual delivery of frailty assessments. This combination of objective and subjective data allows for more accurate capture of frailty in our population, as some older patients may overestimate their actual physical abilities and vice versa, and patient-reported assessments alone may not be as valid in older patients as compared to younger patients.[32] Our findings support this, as 90% of our cohort rated themselves as having a "healthy" Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, despite the fact that approximately 40-70% were classified as pre-frail or frail by the cumulative deficit and phenotypic frailty assessments. These data also reinforce the view that geriatrics-based frailty tools are more sensitive than ECOG at detecting aging-related vulnerability in older patients with cancer.[5]

Moreover, evidence suggests that the use of both patient-reported and objective measures spanning multiple health domains offers the most reliable predictive performance with respect to clinical outcomes such as mortality.[33] The fact that such a large number of patients in their late 70s and even 80s (patients age ≥80 years formed nearly a third of our population) were able to complete these multi-domain assessments indicates that older patients are able to complete rigorous functional evaluations while also receiving care for their blood cancers. Although both cumulative deficit and phenotypic frailty tools may require more time to administer than briefer disease-specific frailty and prognostic scores, like the IMWG-FS, the additional information better classifies frailty and predicts clinical outcomes, especially in older, complex populations treated outside of clinical trials. Our group has previously demonstrated that the cumulative deficit index better stratifies frailty with less ceiling effects compared to the IMWG-FS, which often results in saturation in higher frailty levels based on its age criteria alone.[34] Phenotypic frailty better stratifies survival compared to the IMWG-FS,[35] and gait speed improves the predictive power of disease-based prognostic indices like the International Prognostic Index in DLBCL.[36] Other disease-specific scores, like the Cumulative Illness Rating Scale in chronic lymphocytic leukemia,[37] focus mostly on comorbidity, which is only one domain affecting older adult physiologic reserve in the multidimensional construct of frailty.

More fundamentally, the additional value of established

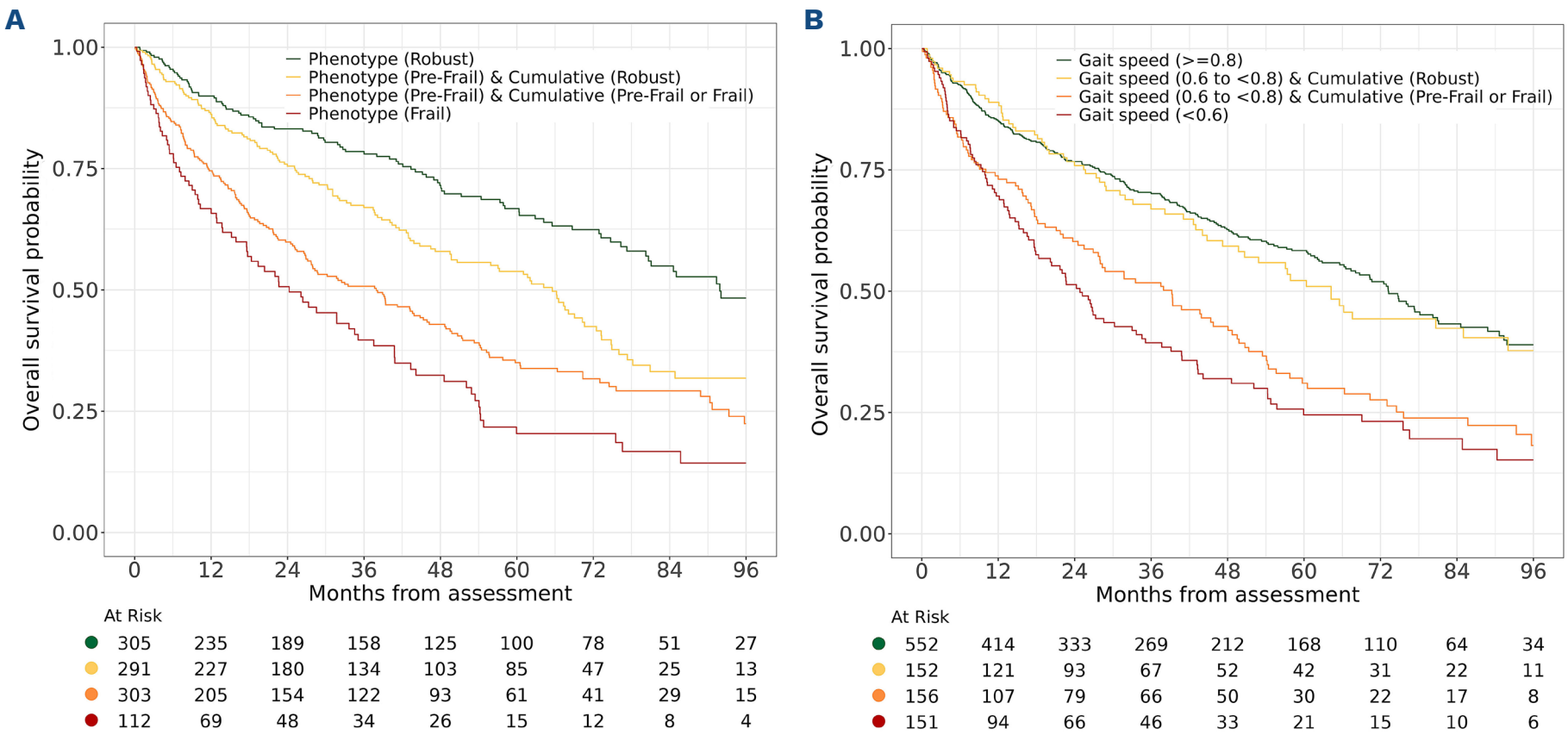


Figure 4. Kaplan-Meier estimates of overall survival, with each frailty measure further stratified by the cumulative deficit index. (A) Patients classified by phenotypic frailty and the cumulative deficit index. (B) Patients classified by usual gait speed and the cumulative deficit index.

geriatrics frailty tools resides not only in the ability to risk stratify at the population level, but also in their ability to guide individualized clinical decision making, both with respect to informing treatment intensity and supportive care interventions. For example, in an 80-year-old female with newly diagnosed multiple myeloma, her age alone would classify her as frail when evaluated by the IMWG-FS, even if she has minimal comorbidities and was independent in her ADL and IADL. If her wish is to pursue treatment that maximizes cancer control and survival, then the IMWG-FS puts her at risk of undertreatment. In contrast, the cumulative deficit index would appropriately classify her as robust, suggesting she can tolerate standard 3-drug, potentially even 4-drug regimens that offer the best benefit in the context of her goals. Now consider the same 80-year-old patient but with early undiagnosed dementia beginning to affect her IADL. She would still be classified as frail when evaluated by the IMWG-FS, but the objective memory tests in the cumulative deficit frailty evaluation would reveal this cognitive impairment, triggering additional family or formal supports to help her adhere to complex medication protocols and follow-up appointments. As patients are surviving longer with treatment improvements in multiple myeloma and other blood cancers, relying on scores such as the IMWG-FS may fail to capture many non-oncologic, aging-related deficits that will become more prevalent and influential in determining outcomes. Notably, the evidence supporting the effectiveness of frailty-guided care in oncology largely supports more multi-domain, comprehensive frailty assessments in line with the cumulative deficit frailty model.[38,39] Although it is not possible on a population level (such as in our study) to account for cancer-related *versus* aging-related drivers of health deficits constituting patient frailty, more comprehensive frailty assessment on

Table 3. Cox proportional hazards models for risk of mortality by disease clinic.

Variable	Lymphoma N of patients=410 N of deaths=169		Leukemia N of patients=230 N of deaths=161		Myeloma N of patients=189 N of deaths=101	
	HR*	95% CI	HR*	95% CI	HR*	95% CI
Cumulative deficit index						
Robust	-	-	-	-	-	-
Pre-frail	2.13	1.53, 2.98	1.89	1.33, 2.68	1.20	0.75, 1.92
Frail	4.17	2.50, 6.96	1.93	1.16, 3.21	1.89	1.09, 3.26
Phenotypic frailty						
Robust	-	-	-	-	-	-
Pre-frail	1.78	1.19, 2.64	1.94	1.26, 3.00	1.65	1.01, 2.71
Frail	3.42	1.98, 5.91	2.46	1.34, 4.53	2.42	1.30, 4.51
Phenotypic frailty + cumulative deficit indices						
Phenotype (robust)	-	-	-	-	-	-
Phenotype (pre-frail) + cumulative (robust)	1.23	0.78, 1.96	1.69	1.03, 2.74	1.62	0.92, 2.85
Phenotype (pre-frail) + cumulative (pre-frail or frail)	2.46	1.61, 3.78	2.19	1.38, 3.49	1.69	0.96, 2.96
Phenotype (frail)	3.58	2.07, 6.18	2.50	1.36, 4.59	2.42	1.30, 4.52
Usual gait speed, m/s						
≥0.8	-	-	-	-	-	-
0.6 to <0.8	1.91	1.34, 2.72	0.89	0.62, 1.27	1.51	0.91, 2.49
<0.6	3.49	2.27, 5.39	1.29	0.79, 2.08	1.65	0.97, 2.82
Usual gait speed + Cumulative deficit index						
Gait speed (≥0.8)	-	-	-	-	-	-
Gait speed (0.6 to <0.8) + cumulative (robust)	1.22	0.74, 1.99	0.69	0.41, 1.16	1.32	0.70, 2.49
Gait speed (0.6 to <0.8) + cumulative (pre-frail or frail)	2.83	1.88, 4.26	1.04	0.69, 1.58	1.74	0.94, 3.23
Gait speed (<0.6)	3.63	2.36, 5.59	1.31	0.81, 2.12	1.66	0.98, 2.83
Usual gait speed per 0.1 m/s decrease	1.19	1.12, 1.27	1.04	0.97, 1.13	1.05	0.99, 1.13
During the last week, on how many days did you walk outside?						
≥3 days	-	-	-	-	-	-
<3 days	1.66	1.10, 2.51	2.00	1.24, 3.22	0.95	0.53, 1.72
Was the patient dependent on the assistance of others to complete the assessment?						
Without help	-	-	-	-	-	-
With help or unable	0.96	0.59, 1.56	1.41	0.84, 2.37	2.03	1.12, 3.69

*Hazard ratios for each variable in the table are from separate models with adjustment for age, sex, and treatment intensity.

an individual level can guide clinicians to consider whether treating a patient's cancer could be tolerated or even improve their frailty.[40]

Another strength of our study lies in the use of multiple established frailty assessments collected in each patient allowing us to compare aspects of frailty assessment within and outside our cohort. The proportion of patients in our blood cancer cohort classified as pre-frail and frail by phenotypic frailty assessment is higher than most studies of general populations.[41] The distribution of gait speed is also lower.[15] In particular, impaired mobility, weakness, and weight loss were more prevalent in our cohort than in general populations of community-dwelling adults; for example, 32% of OHM patients reported weight loss, compared to only 6% of the population in the original Fried phenotype study.[14] This increased prevalence may be in part due to the older age of our population, but the systemic nature of blood cancers and their multiorgan involvement may deplete physiologic reserve more rapidly than in other chronic, aging-related conditions that affect older patients.

The results of our comparative analyses of frailty assessment tools are provocative. The cumulative deficit index, phenotypic frailty, and gait speed all strongly predicted mortality but yielded different classifications in a portion of patients (Figure 2). This difference in classification reinforces the need for caution in order to avoid treatment decisions based on one assessment of frailty status alone: a patient labeled frail by one method may be labeled pre-frail or even robust by a different method. On this point, we found that a subgroup of patients classified as pre-frail by phenotypic frailty were reclassified as either robust or pre-frail/frail by the cumulative deficit index. The worse survival in this subgroup reclassified as pre-frail/frail suggests that the specific nature of health deficits may further explain differences in underlying vulnerability and risk beyond frailty status alone. Whether these deficits are modifiable, and whether their additive effect presents the harm resulting from a given cancer treatment to be greater than its benefits, and whether the harm/benefit ratio are consistent with a patient's values and goals should all ultimately guide treatment.[42] This argument supports a "screen first" or longitudinal monitoring strategy with briefer tools, followed by a full cumulative deficit frailty assessment for further triage and interventions.

Whether frailty assessment not only predicts outcomes but also improves them represents an urgent area of investigation in older adults with blood cancers.[43] Innovative delivery methods are needed to make frailty assessments more feasible in busy oncology settings to allow them to be implemented earlier in treatment decisions and more frequently in follow-up. Virtual assessments administered to patients entirely in their homes provide one example.[16,44-46] Digital health technology,[47,48] such as wearable devices[49] and smartphones,[50] also expands the ability to capture objective performance measures of frailty (e.g., gait speed) and to monitor these measures over time.[51] Moreover, sophisticated administrative- and electronic health record-based frailty assessments provide another area of promise.[52-54] Such advances in the delivery of frailty assessments are needed to enhance their adoption and fidelity, prerequisites to ensure their effectiveness in improving treatment decisions and optimizing supportive care. Although they overcome time and resource constraints, innovations in frailty assessment should ideally be validated against cumulative deficit or phenotypic frailty standards to maintain construct validity.

There are limitations to our study. The prevalence of frailty measured in our population at Dana-Farber, an academic tertiary care center, is likely lower than the prevalence of frailty in patients seen in community oncology practices. Although this difference in prevalence may not affect associations with mortality, we also assessed frailty at the first oncology consultation, which varied from new diagnosis for a blood cancer to relapsed or refractory disease. We were unable to more completely control for this heterogeneity in "time 0" of when patients began follow-up in our study, or the heterogeneity of cancer subtypes and treatments across the leukemia, lymphoma, and multiple myeloma clinics. For example, the 337 patients classified as "supportive care" for their treatment intensity could have been on supportive care regimens without active cancer treatment either because of an indolent disease not requiring therapy or because a patient was deemed by their oncologist as unable to tolerate treatment; these distinctions and rationale were not always apparent in the clinical documentation we reviewed. Variability in the timing of our frailty assessment relative to each patient's disease course could also help explain the lack of association between gait speed and mortality in leukemias, especially in relation to the stronger association in the lymphomas. Many leukemias are aggressive with high short-term mortality that could obscure the predictive contribution of gait speed in smaller numbers, whereas many lymphomas are more indolent and/or treatment responsive, with longer life expectancies that may allow brief frailty measures to better discriminate risk. Other studies designed and powered specifically to measure gait speed and other physical performance tests at uniform timepoints in leukemia (e.g., newly diagnosed AML) have found these markers of frailty to be strongly predictive of mortality and other clinical outcomes.[26,27]

We also did not measure other outcomes, other than survival, that are also important in older adults, such as quality of life. Future work should further investigate how deficit accumulation frailty, phenotypic frailty, and gait speed relate to treatment tolerance, toxicity, functional decline, and receipt of disease-modifying therapy. Although mortality is a clinically unambiguous endpoint that reflects downstream consequences of frailty, more detailed measurement of patient-centered outcomes will further elucidate quality of life

on treatment in frail patients and the mechanisms by which frailty leads to inferior outcomes.[55] Decentralized, virtual assessments of frailty and patient-centered outcomes that are validated for construct and predictive properties may be more feasible to achieve these ends in future studies.

In conclusion, our study provides compelling evidence regarding gold standard frailty assessment tools and their impact on long-term survival in older adults with blood cancers. In the context of sufficient time and resources, the cumulative deficit index provides the most information to accurately risk-stratify patients and identify health deficits for intervention. In busy clinical settings, however, brief assessments such as phenotypic frailty, 4-meter gait speed, or even single-item questions (e.g., asking how many days of the week an older patient walks outside) can identify vulnerable patients at high risk of death. Innovations in the delivery of frailty assessments will bridge the gap between their demonstrated value and practical feasibility, and our paper provides a benchmark against which these innovations can be compared.

Disclosures

No conflicts of interest to disclose.

Contributions

CD, JAD and GAA are responsible for study concept and design, and data collection and curation. AMC is responsible for study concept and design, data collection and curation, and formal analysis. TTH, AS, LM and MA are responsible for data collection and curation. All authors interpreted the data and contributed to writing the manuscript.

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Data-sharing statement

Data requests will be considered on a case-by-case basis and in accordance with the regulations of the Dana-Farber Harvard Cancer Center Office for Human Research Studies. Please contact: gregory_abel@dfci.harvard.edu

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