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

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Abstract

Geriatric assessment is recommended for older adults undergoing cancer treatment, but the best frailty assessment tools for blood cancers are unknown. We conducted a prospective cohort study of three gold standard approaches: the cumulative deficit index, phenotypic frailty, and four-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 1011 patients underwent frailty assessment with a median age of 78 years (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 the robust. 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 (ages 65+) 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” into one measure the geriatric assessment of medical comorbidities, cognition, and function—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 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 a 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 teased out 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 75 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 (ADLs/IADLs), 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 **Supplemental Methods** and **Supplemental Table 1**. 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 similarly compared to the in-person assessments, although they may select to some degree 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, 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 pre-cancer underlying fitness, impact of the cancer, and toxicity of cancer treatment. These factors are difficult to disentangle, since cancer-related factors may be collinear and/or intermediate variables. For this reason, 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), 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. 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 1011 patients (**Figure 1**). Median age was 78 years (interquartile range [IQR], 76-82 years) and 36% were female (**Table 1**). Patients with lymphoma represented the largest disease clinic subgroup (410, 41%), followed by leukemia (230, 23%) and multiple myeloma (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. **Figure 2** is a Sankey diagram that illustrates the degree to which the cumulative deficit index reclassified patients first categorized by phenotypic frailty and gait speed (distribution of patients in **Supplemental Table 5**). 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 vs. 75 months for robust patients, compared to 24 months in patients identified as frail by phenotypic frailty vs. 92 months for robust patients (**Supplemental Table 6**). Patients in the slowest gait speed category (< 0.6 m/s) had a median survival of 25 months vs. 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 hazard of 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 whether or not treatment intensity was controlled for in our models (Supplemental Table 4). In general, point estimates of hazard ratios 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 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 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 geriatrics 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 1000 older patients with blood cancers assessed over 10 years, our data contribute a definitive and novel analysis of the prevalence of frailty in this population and a unique assessment of three tools' comparative utility. 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 AML[22], MDS[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 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 evidence mounting 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 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, capturing patients underrepresented 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 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 ~ 90% classified as pre-frail or frail by both the cumulative deficit and phenotypic frailty assessments. These data also reinforce 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] 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 argues 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 take additional 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 saturates 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 CLL[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 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 ADLs and IADLs. 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 three-drug, potentially even four-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 IADLs. 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 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 vs. aging-related drivers of health deficits constituting patient frailty, more comprehensive frailty assessment on an individual level can guide clinicians regarding whether treating a patient’s cancer could be tolerated or even improve their frailty.[40]

Another strength of our study pertains to 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 relative to 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: e.g., 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 more rapidly deplete physiologic reserve than 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 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. To 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, whether their additive effect renders the harms of a given cancer treatment greater than its benefits, and whether the harm/benefit ratio are consistent with a patient's values and goals should ultimately guide treatment.[42] The argument above 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 implement earlier in treatment decisions and more frequently in follow-up. Virtual assessments administered entirely to patients 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 EHR-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 barriers, innovations in frailty assessment should ideally be validated against the 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, as well as 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 relative 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 important in older adults other than survival, 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, four-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.

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

	Overall N = 1011	**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)					
< 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					
Female	363 (36%)	153 (37%)	74 (32%)	71 (38%)	65 (36%)
Male	648 (64%)	257 (63%)	156 (68%)	118 (62%)	117 (64%)
Patient-reported ECOG PS*					
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**					
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)					
≥ 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					
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					
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%)
Phenotypic frailty: unintentional weight loss	319 (32%)	124 (30%)	83 (36%)	67 (35%)	45 (25%)
Phenotypic frailty: self-reported exhaustion	111 (11%)	33 (8%)	30 (13%)	28 (15%)	20 (11%)
Phenotypic frailty: low energy expenditure	33 (3%)	9 (2%)	8 (3%)	11 (6%)	5 (3%)
Phenotypic frailty: slow gait speed	199 (20%)	87 (21%)	37 (16%)	45 (24%)	30 (16%)
Phenotypic frailty:	533 (53%)	217 (53%)	137 (60%)	88 (47%)	91 (50%)

	Overall N = 1011	**Lymphoma** n = 410	**Leukemia** n = 230	**Myeloma** n = 189	**Other** n = 182
weak grip strength					
During the last week, on how many days did you walk outside?					
≥ 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?					
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?					
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 ECOG performance status 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

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

Frailty measure	**Overall Cohort** N = 1011	
	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 for each variable in the table are from separate models **with adjustment for age and sex**

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

	Lymphoma Number of patients: 410 Number of deaths: 169		**Leukemia** Number of patients: 230 Number of deaths: 161		**Myeloma** Number of patients: 189 Number 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

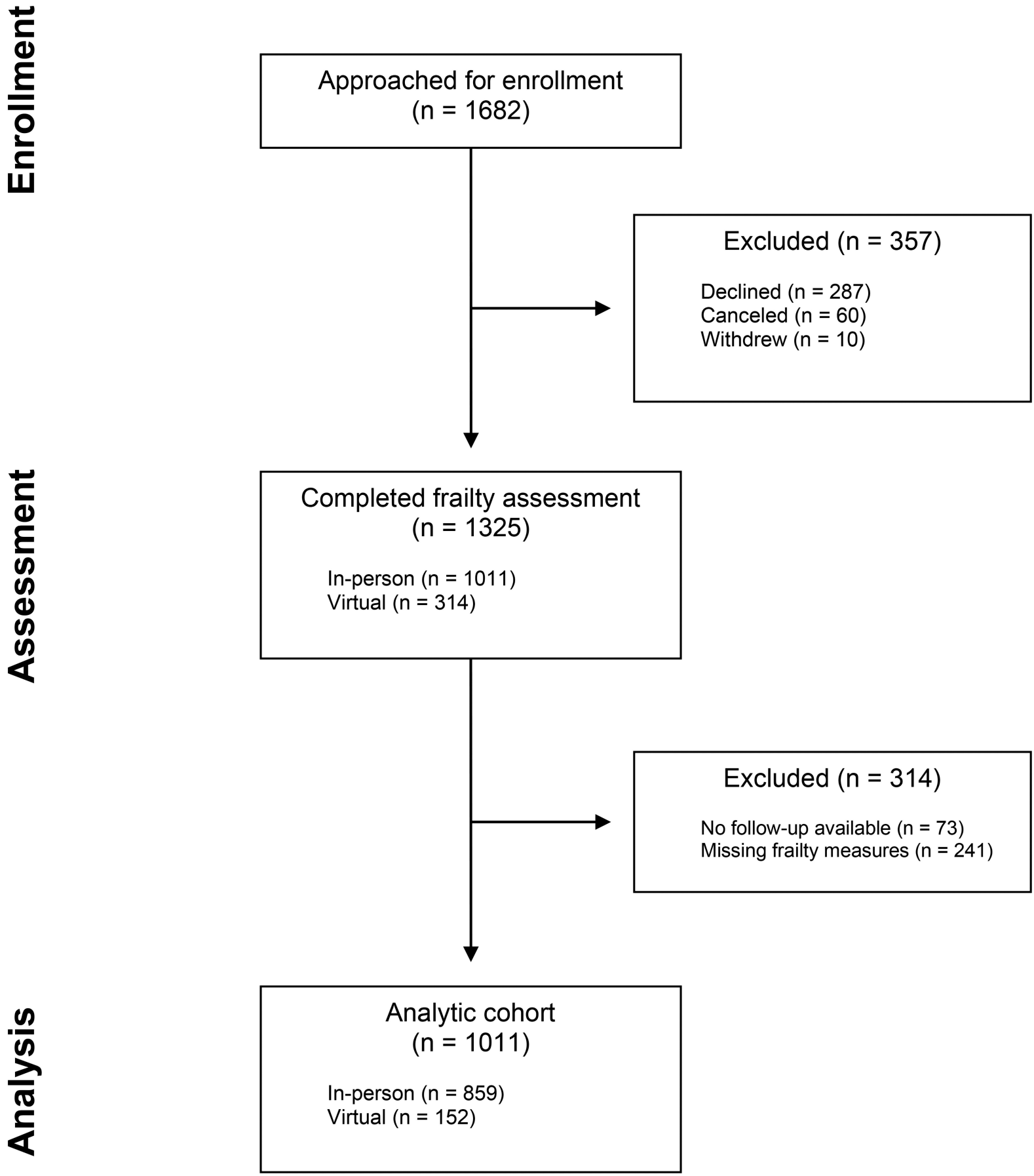
*Hazard ratios for each variable in the table are from separate models **with adjustment for age, sex, and treatment intensity**.

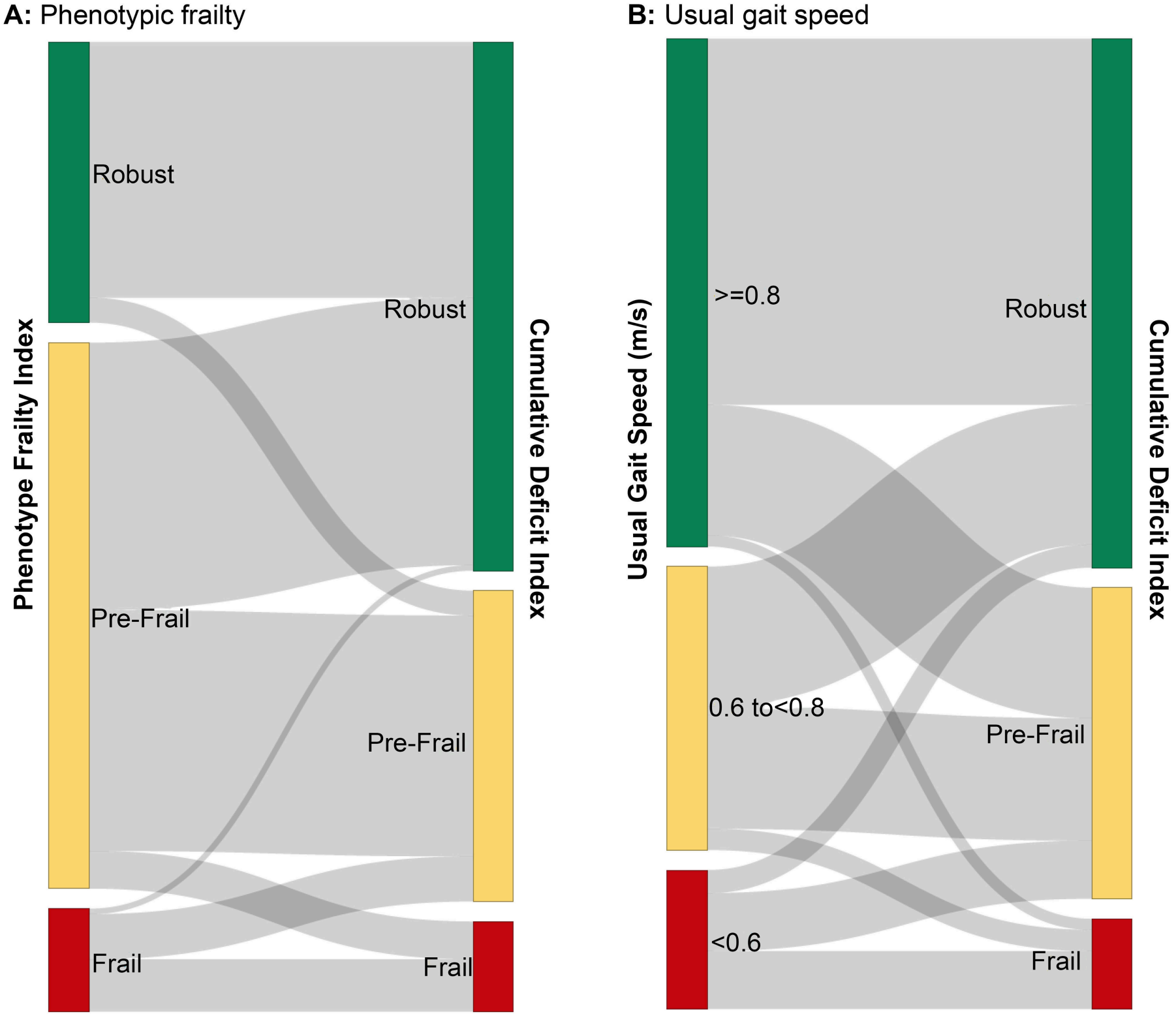
Figure 1: Flow diagram depicting enrollment into study cohort

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. Panel (**A**) presents patients originally classified by phenotypic frailty and panel (**B**) presents patients originally classified by gait speed.

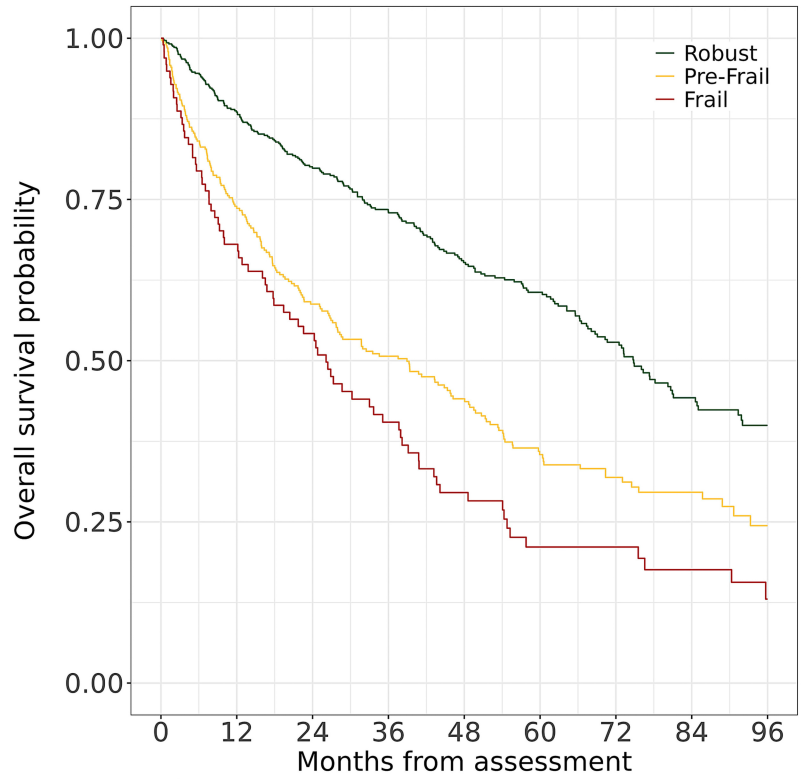
Figure 3: Kaplan-Meier estimates of overall survival, stratified by increasing severity of each frailty measure. Panel (**A**) presents overall survival probability with frailty classified by the cumulative deficit index, panel (**B**) presents overall survival probability with frailty classified by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

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


Enrollment
Approached for enrollment
(n = 1682)
Excluded (n = 357)
Declined (n = 287)
Canceled (n = 60)
Withdrew (n = 10)
Assessment
Completed frailty assessment
(n = 1325)
In-person (n = 1011)
Virtual (n = 314)
Excluded (n = 314)
No follow-up available (n = 73)
Missing frailty measures (n = 241)
Analysis
Analytic cohort
(n = 1011)
In-person (n = 859)
Virtual (n = 152)

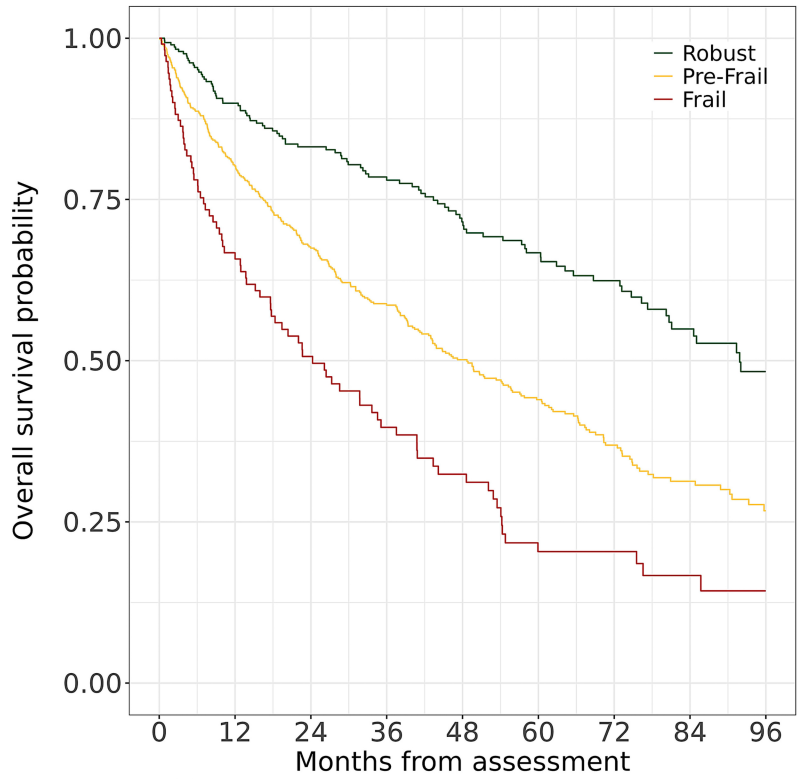

A: Phenotypic frailty
Phenotype Frailty Index
Robust
Pre-Frail
Frail
Robust
Pre-Frail
Frail
Cumulative Deficit Index
B: Usual gait speed
Usual Gait Speed (m/s)
>=0.8
0.6 to<0.8
<0.6
Robust
Pre-Frail
Frail
Cumulative Deficit Index

A: Cumulative deficit index



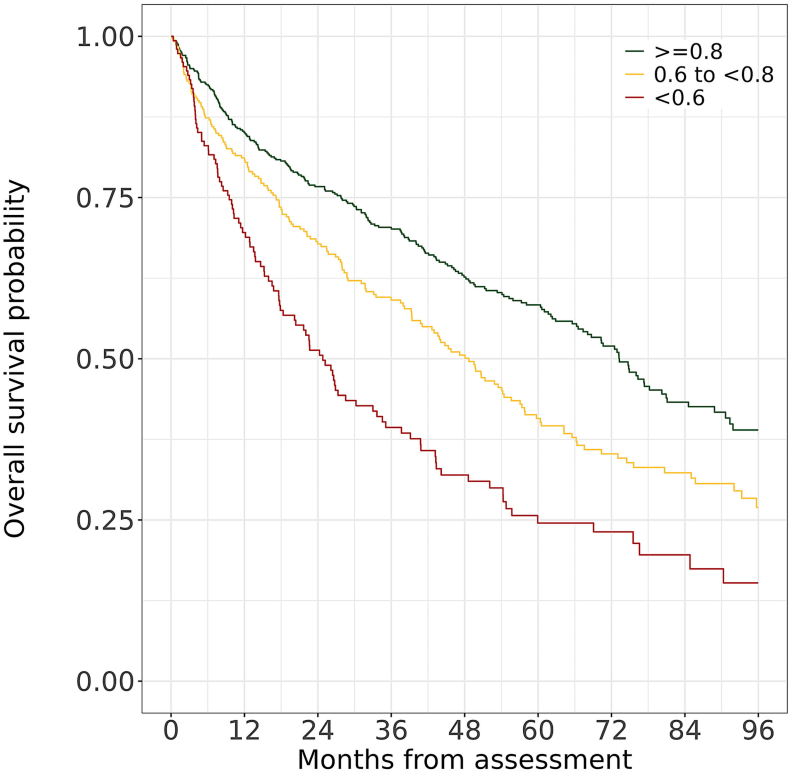
At Risk									
Robust	575	447	359	284	222	178	121	73	40
Pre-Frail	338	224	163	130	101	69	45	31	14
Frail	98	65	49	34	24	14	12	9	5

B: Phenotypic frailty



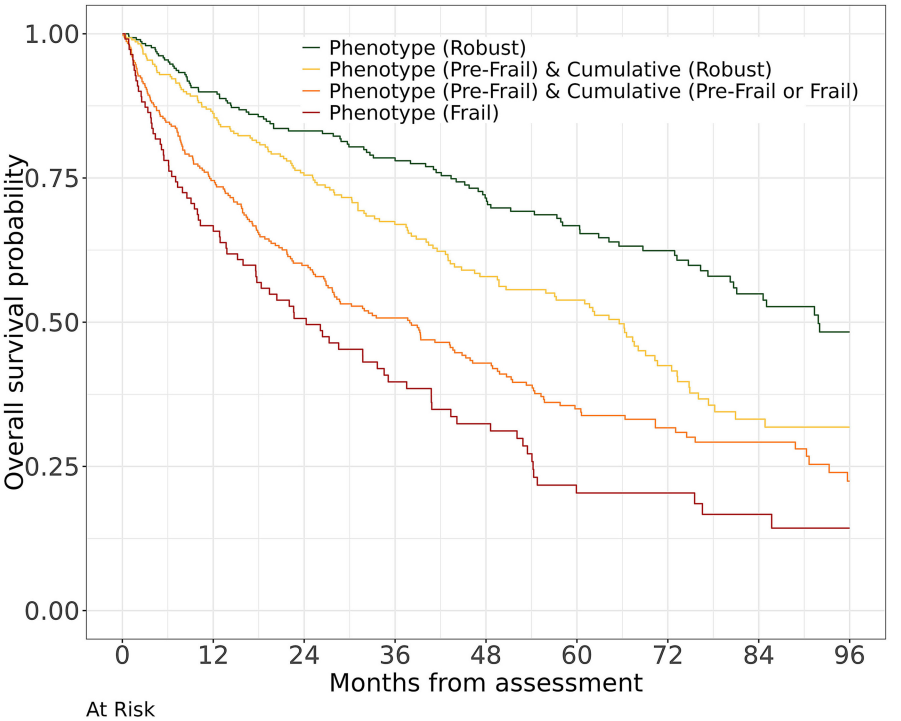
At Risk									
Robust	305	235	189	158	125	100	78	51	27
Pre-Frail	594	432	334	256	196	146	88	54	28
Frail	112	69	48	34	26	15	12	8	4

C: Usual gait speed



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

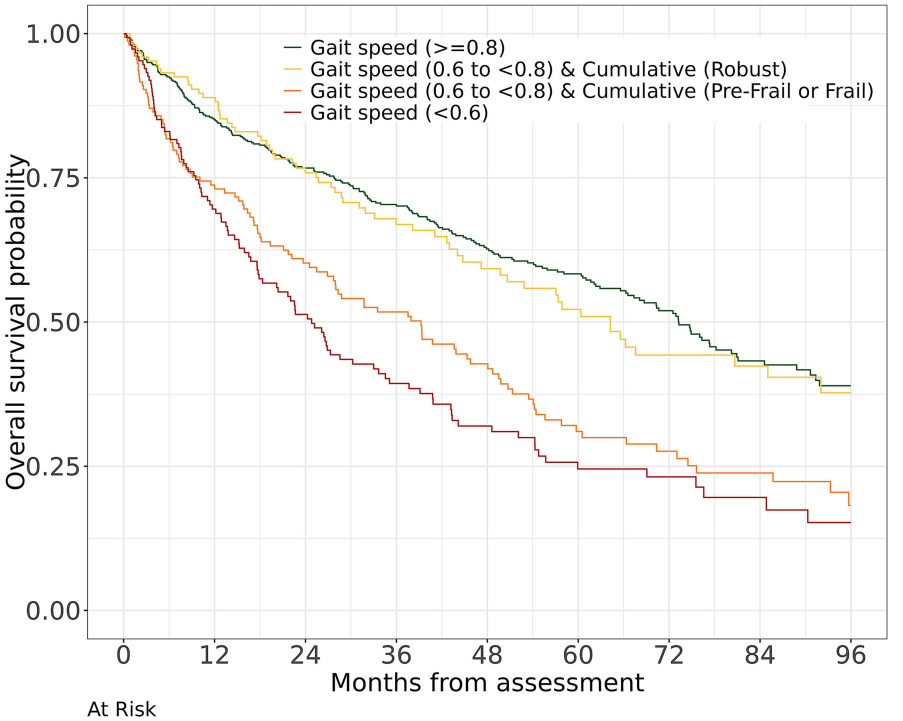
A: Phenotypic frailty



At Risk

305	235	189	158	125	100	78	51	27
291	227	180	134	103	85	47	25	13
303	205	154	122	93	61	41	29	15
112	69	48	34	26	15	12	8	4

B: Usual gait speed



At Risk

552	414	333	269	212	168	110	64	34
152	121	93	67	52	42	31	22	11
156	107	79	66	50	30	22	17	8
151	94	66	46	33	21	15	10	6

Supplemental Methods: Frailty Measures, Covariates, and Overall Survival

Frailty Measures

The OHM Program frailty assessment includes 42 patient-reported and objective performance items spanning the health domains of functional status (ADLs/IADLs), mobility and muscle strength, nutrition, cognition, comorbidity, and social support. We originally conducted assessments in-person with patients as they were seen in the clinics, and in 2020 during the pandemic adapted our clinical assessment to a remote format that can be conducted either over videoconference or telephone. We have previously published that the virtual format leads to similar frailty classification as the clinical format,[1] and we have continued administering the virtual format for patients who preferred it over in-person assessment. Full details of our frailty instrument, the cut points used for each item, and a comparison between in-person and virtual format, are included in **Supplemental Table 1**. The three frailty assessment measures for this analysis were components of this full frailty screening as follows.

Cumulative deficit frailty index *(average time to complete 15-20 minutes)*: We developed our cumulative deficit index adhering to the Rockwood methodology of deficit accumulation frailty.[2] Each item that was scored "positive" in a patient was scored as a health deficit, and the frailty index was the total proportion of deficits present in an individual out of the total number of possible deficits measured. Since the frailty index is a continuous measure (range 0-1), we classified patients as robust (0 to < 0.2), pre-frail (0.2 to < 0.35), and frail (≥ 0.35-1), consistent with cut points frequently used in cancer populations.[3] A minimum of 30 deficits measured is generally recommended as necessary to calculate a frailty index, and all patients in our cohort met that minimum threshold. For our study of frailty tools, we considered the cumulative deficit frailty index as the reference standard since it is based on a comprehensive geriatric assessment, includes all domains important in older adult health, and also identifies the most deficits that might be optimized with supportive care interventions.

Fried phenotypic frailty *(average time to complete 5-10 minutes)*: The phenotypic model uses five criteria to define a frailty syndrome: slow gait speed, weakness measured by grip strength, self-reported exhaustion, low physical activity, and weight loss.[4] Patients were classified as robust if they had no deficits, pre-frail if they had one or two deficits, and frail if they had three or more deficits. Patients without all five deficits collected were excluded as having insufficient data for frailty classification.

4-meter gait speed *(referred to as "gait speed"; average time to complete 1-2 minutes)*: Gait speed was obtained using the National Institutes of Health 4-meter gait speed test[5] as part of our full frailty assessment. From a standing start, participants were asked to walk at a usual pace (normal gait speed) for 4 meters using distinct landmarks, and the speed was recorded in meters per second (m/s) using a stopwatch. Consistent with prior literature, we used cutoffs of declining gait speed that correspond to worsening mobility and frailty: ≥ 0.8 m/s, ≥ 0.6 to < 0.8 m/s, and < 0.6 m/s.[6] We also analyzed gait speed as a continuous measure.

Single item frailty measures *(average time to complete each < 1 minute)*: From our 42-item assessment, we also considered three single-item measures as summary measures of frailty: days walked outside during the last week (3 or more days; less than 3 days), ability to explain the reason for presentation to DFCI (without help; with help or unable), ability to complete the assessment (without help; with help or unable).

For virtual measurement of the objective performance measures used in the above frailty assessment tools, grip strength was replaced with the self-reported item, "Do you have difficulty gripping with your hands (e.g. opening a jar), yes or no?"[7] For short-term memory, the well-validated 5-item recall from the Montreal Cognitive Assessment (MoCA)[8] was used given its ease of administration over videoconference or telephone. For executive function and visuospatial ability, the Clock-in-the-Box test[9] was changed to a simple clock draw test that the patient completes and displays to the camera for scoring or if video is not available, mails to the research team. Gait speed was collected by the research assistant over video by training a patient's caregiver to administer the test to the patient with a stopwatch and a 4-meter strip of ribbon that was sent by mail.[1] If video was unavailable, then a patient's subjective assessment of his/her gait speed was used instead by asking the question, "Which of the following best describes your usual walking pace: slow, steady average, or fast?"[7]

Covariates

We assessed from chart review each patient's age, sex, disease clinic in which they were seen at Dana-Farber (leukemia, lymphoma, and multiple myeloma), and the disease subtype (e.g., diffuse large B-cell lymphoma). Since the Dana-Farber hematologic oncology clinics also see consultations for precursor (e.g., MGUS and CCUS), indolent (e.g., some myeloproliferative neoplasms), and rarely, benign hematologic conditions, we grouped any condition deemed not to be an active blood cancer into a category of "other". The distribution of patients across disease clinics and disease subtypes is presented in **Supplemental Table 2**. For the active blood cancer subtypes, we abstracted cancer treatments recommended by the hematologic oncologist during the initial consultation. Cancer treatments were assigned an initial treatment intensity—higher intensity, lower intensity, and supportive care—by a geriatrician with expertise in geriatric oncology. Treatment assignments were then reviewed by disease experts in leukemia, lymphoma, and multiple myeloma, with any discrepancies discussed and resolved among the members of the study team through consensus (see Supplemental Table 3).

Overall Survival

We leveraged a large, health system–based cohort in which survival could be reliably ascertained across clinics and hospitals. We assessed overall survival via patient vital status recorded in our electronic health record system (EHR; linked to several area hospital systems) and supplemented these data with

mortality data from the National Death Index[10] (with mortality data complete up to 2020). For patients receiving care not captured in our EHR, we confirmed vital status via phone calls to patients' primary care clinics. We excluded patients who had no evidence of follow-up in our EHR after their initial consultation visit at Dana-Farber. Patients were censored on the date they were last confirmed alive, via either their last vital status check or their last clinic visit recorded in our EHR.

Supplemental Table 1: Patient-reported and objective performance measures constituting our in-person and virtual frailty assessments for older adults with hematologic malignancies

Domain	Measured Variable	Scoring	In-person Measurement Method	Virtual Measurement Method
Function	1. Bathing 2. Dressing 3. Getting in/out of chair 4. Walking around house 5. Eating 6. Grooming 7. Using Toilet 8. Shopping 9. Doing housework 10. Meal preparations 11. Taking medication 12. Handling finances	"Without help" = 0; "With help or unable" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
	13. Days outside in the last week	≥ 3 days = 0; < 3 days = 1		
	14. Self-report ECOG PS	0 = 0; 1-2 = 0.5; 3-4 = 1		
	15.Self-rating of health	"Excellent" = 0; "Very good" = 0.25; "Good" = 0.5; "Fair" = 0.75; "Poor" = 1		
	16. How health has changed in last year	"Same/Better" = 0; "Worse" = 1		
	17. Stayed in bed at least half the day due to health in last month 18. Cut down on usual activity in last month	"No" = 0; "Yes" = 1		
	19. How often feel everything is an effort 20. How often have trouble getting going	"Rarely" = 0; "Some of time" = 0.5; "Most of time" = 1		
Physical (Mobility)	21. Getting up/downstairs	"Without help" = 0; "With help or unable" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
	22. Rapid pace walk speed	Objective measure: < 0.61 m/s = 1	Objective measure: NIH 4-meter gait speed test administered by research assistant	Objective measure: NIH 4-meter gait speed test administered by caregiver at home
	23. Usual pace walk speed	Objective measure: < 0.38 m/s = 1 Self-report:	Objective measure: NIH 4-meter gait speed test administered by research assistant	Objective measure: NIH 4-meter gait speed test administered by caregiver at home AND Self-report:

		"Fast" or "Steady Average" = 0; "Slow" = 1		Estimated using following self-report question: *Which of the following best describes your usual walking pace? Slow, Steady average, or Fast.*
Physical (Muscle Function)	24. Lifting 10 lbs	"Without help" = 0; "With help or unable" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
	25. Grip strength	Grip strength (GS) in kg: Men, score = 1 only if: BMI ≤ 24 and GS ≤ 29 BMI 24.1-28 and GS ≤30 BMI > 28 and GS ≤ 32 Women, score = 1 only if: BMI ≤ 23 and GS ≤ 17 BMI 23.1-26 and GS ≤17.3 BMI 26.1-29 and GS ≤18 BMI > 29 and GS ≤ 21 OR Self-report: "No" = 0; "Yes" = 1	Jamar Hand Dynamometer grip strength test[11]	Estimated using the following self-report question: *Do you have difficulty gripping with your hands (e.g. opening a jar)?*
Physical (Nutrition)	26. Lost more than 10 lbs in last year unintentionally	"No" = 0; "Yes" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
	27. BMI	≥ 18.5, < 25 = 0; ≥ 25, < 30 = 0.5; < 18.5, ≥ 30 = 1	Pulled from patient medical record	Pulled from patient medical record
Social Support	28. How often feel lonely	"Rarely" = 0; "Some of time" = 0.5; "Most of time" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
Psychological (Mood)	29. How often feel depressed	"Rarely" = 0; "Some of time" = 0.5; "Most of time" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
Psychological (Cognition)	30. How often feel happy	"Most of time" = 0; "Some of time" = 0.5; "Rarely" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire
	31. MoCA 5-word delayed recall[12]	5 = 0; 4 = 0.25; 3 = 0.5; 2 = 0.75; 0 or 1 = 1	Administered by research assistant	Administered by research assistant
	32. Clock-in-the-Box (CIB)[9] or Clock Drawing	8 = 0; 7 = 0.25, 6 = 0.5; 5 = 0.75; 0-4 = 1 (CIB) OR 7 = 0; 6 = 0.25, 5 = 0.5; 4 = 0.75; 0-3 = 1 (Clock Draw)	CIB test administered in person	Adapted Clock Draw administered over phone or video
	33. Ability to explain presentation to DFCI 34. Ability to complete assessment without assistance of others	"Without help" = 0; "With help or unable" = 1	Assessed by research assistant	Assessed by research assistant
Comorbidity	35. High blood pressure 36. Heart attack 37. CHF 38. Stroke 39. Cancer 40. Diabetes	"Never had" = 0 "Not sure" = 0.5 "Have/have had" = 1	Self-reported using patient questionnaire	Self-reported using patient questionnaire

	41. Arthritis 42. Chronic Lung Disease			
Cumulative Deficit Frailty Score[13]	Sum all points given for each deficit above and divide by number of total points possible	Cut-points: < 0.2 = Robust 0.2 to < 0.35 = Pre-Frail ≥ 0.35 = Frail		
Phenotypic Frailty Score[4]	Sum all points given for the following five items only: physical activity (#4), exhaustion (#19,20*), usual gait speed ≤ 0.65 m/s**), grip strength (#25), and unintentional weight loss (#26). *For in-person and virtual scoring of exhaustion, 1 point is given only if “Most of time” is answered for either or both #19 and #20. Otherwise, score is zero for this item. **For in-person scoring of gait speed, #22 should be scored. For virtual scoring of gait speed, #22 should be scored when caregiver-administered walk test data are available; if caregiver-administered walk test data are not available, #23 self-reported gait speed should be scored.	Cut-points: 0 = Robust 1-2 = Pre-Frail 3-5 = Frail		

Supplemental Table 2: Disease Classifications

Disease subtype	All patients (N=1011)
Leukemia	230
Myelodysplastic syndrome (MDS)	110
Acute myeloid leukemia (AML)	48
Chronic myelomonocytic leukemia (CMML)	25
Chronic myeloid leukemia (CML)	21
Myelofibrosis (MF)	19
Acute lymphoblastic leukemia (ALL)	4
Chronic neutrophilic leukemia (CNL)	2
Blastic plasmacytoid dendritic cell neoplasm (BDPCN)	1
Lymphoma	410
Non-Hodgkin's lymphoma (NHL)	403
Chronic lymphocytic leukemia (CLL)	97
Waldenstrom macroglobulinemia (WM)	85
Diffuse large B-cell lymphoma (DLBCL)	72
Follicular lymphoma (FL)	43
Other unspecified non-Hodgkin's lymphoma (other NHL)*	34
Marginal zone lymphoma (MZL)	28
Mantle cell lymphoma (MCL)	23
Small lymphocytic leukemia (SLL)	7
Angioimmunoblastic T-cell lymphoma (AITL)	3
Mucosa-associated lymphoid tissue lymphoma (MALT)	3
T-cell prolymphocytic leukemia (T-PLL)	3
Hairy cell leukemia (HCL)	2
B-cell prolymphocytic leukemia (B-PLL)	1
Prolymphocytic leukemia (PLL)	1
Small marginal zone lymphoma (SMZL)	1
Hodgkin's lymphoma (HL)	7
Myeloma	189
Multiple myeloma (MM)	170
Smoldering multiple myeloma (SMM)	19
Other	182
Other hematologic disorders‡	109
Monoclonal gammopathy of undetermined significance (MGUS)	59
Myeloproliferative neoplasm (MPN)	14

*Other NHL includes all forms of non-Hodgkin's lymphoma that were not further classified during the initial consultation

‡Other hematologic disorders include primary amyloidosis (AL), anemia, essential thrombocythemia (ET), monoclonal B-cell lymphocytosis, pancytopenia, polycythemia vera (PV), and other small groups of benign conditions

Supplemental Table 3: Intensity of Systemic Therapy Classifications by Disease

Disease Subtype	Systemic Therapy Intensity		
Leukemia	Supportive care	Lower intensity	Higher intensity
Myelodysplastic syndrome (MDS)	Erythropoietin stimulating agent (ESA) Luspatercept Monitoring Supportive care	Hydroxyurea Hypomethylating agent (HMA)-based regiments with/without venetoclax Other single agent treatments	Hematopoietic cell transplantation (HCT) Investigational drug in clinical trial
Acute myeloid leukemia (AML)	Monitoring Supportive care	Hydroxyurea HMA-based regiments with/without venetoclax Investigational drug in clinical trial Other single agent treatments	Investigational drug in clinical trial*
Chronic myelomonocytic leukemia (CMML)	ESA Monitoring	Hydroxyurea HMA-based regiments with/without venetoclax	Investigational drug in clinical trial
Chronic myeloid leukemia (CML)	Monitoring	Investigational drug in clinical trial Tyrosine kinase inhibitor (TKI)-based regimens	No patients in this category
Acute lymphoblastic leukemia (ALL)	No patients in this category	No patients in this category	Chemotherapy-based regimens TKI-based regimens
Chronic neutrophilic leukemia (CNL)	No patients in this category	Hydroxyurea	None
Blastic plasmacytoid dendritic cell neoplasm (BDPCN)	No patients in this category	None	Investigational drug in clinical trial
Lymphoma	Supportive care	Lower intensity	Higher intensity
Chronic lymphocytic leukemia (CLL)	Monitoring Radiation therapy	Anti-CD20 monotherapy Other single agent treatments Venetoclax	Anti-CD20 multi-drug regimens** BTKI-based regimens PI3Kδ inhibitor-based regimens
Waldenstrom macroglobulinemia (WM)	ESA Monitoring Supportive care	Bruton tyrosine kinase inhibitor (BTKI)-based regimens Targeted therapy or immunotherapy-based regimens	Chemoimmunotherapy
Diffuse large B-cell lymphoma (DLBCL)	No patients in this category	Anti-CD20 monotherapy	Anti-CD20 multi-drug regimens** CAR T-cell therapy
Follicular lymphoma (FL)	Radiation therapy	Anti-CD20 monotherapy	Anti-CD20 multi-drug regimens** CAR T-cell therapy

			Multi-drug chemotherapy PI3Kδ inhibitor-based regimens
Other unspecified non-Hodgkin's lymphoma (other NHL)	Monitoring	No patients in this category	Multi-drug chemotherapy
Marginal zone lymphoma (MZL)	Monitoring Radiation therapy Splenectomy	Anti-CD20 monotherapy	Anti-CD20 multi-drug regimens**
Mantle cell lymphoma (MCL)	Monitoring	Anti-CD20 monotherapy	Anti-CD20 multi-drug regimens** BTKI-based regimens
Small lymphocytic leukemia (SLL)	Monitoring	No patients in this category	Anti-CD20 multi-drug regimens**
Angioimmunoblastic T-cell lymphoma (AITL)	No patients in this category	No patients in this category	Anti-CD30 multi-drug regimens
Mucosa-associated lymphoid tissue lymphoma (MALT)	Monitoring Radiation therapy	No patients in this category	None
T-cell prolymphocytic leukemia (T-PLL)	No patients in this category	No patients in this category	Anti-CD52 monotherapy
Hairy cell leukemia (HCL)	No patients in this category	No patients in this category	None
B-cell prolymphocytic leukemia (B-PLL)	No patients in this category	No patients in this category	BTKI-based regimens
Prolymphocytic leukemia (PLL)	Monitoring	No patients in this category	No patients in this category
Small marginal zone lymphoma (SMZL)	Monitoring	No patients in this category	No patients in this category
Myeloma	Supportive care	Lower intensity	Higher intensity
Multiple myeloma (MM)	Monitoring Supportive care	Doublet therapy***	Triplet or quadruplet therapy****

*No patients with AML were treated with inpatient induction regimens (e.g., 7+3)
**Examples of anti-CD20 multi-drug regimens included R-CHOP and R-GemOx
***Examples of doublet regimens included combinations such as lenalidomide-dexamethasone (Rd) and bortezomib-dexamethasone (Vd)
****Examples of triplet regimens included combinations such as bortezomib-lenalidomide-dexamethasone (RVd) and daratumumab-lenalidomide-dexamethasone (DRd); quadruplet regimens included combinations such as daratumumab-lenalidomide-bortezomib-dexamethasone (DRVd)

Supplemental Table 4. Cox proportional hazards models for risk of mortality by disease clinic. Hazard ratios for each variable in the table are from separate models with adjustment for age and sex, but not treatment intensity.

	Lymphoma Number of patients: 410 Number of deaths: 169		Leukemia Number of patients: 230 Number of deaths: 161		Myeloma Number of patients: 189 Number of deaths: 101	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Cumulative deficit index						
Robust	—	—	—	—	—	—
Pre-Frail	2.18	1.57, 3.04	1.97	1.39, 2.80	1.23	0.78, 1.95
Frail	4.39	2.63, 7.31	1.71	1.04, 2.82	1.78	1.04, 3.06
Phenotype frailty index						
Robust	—	—	—	—	—	—
Pre-Frail	1.79	1.20, 2.66	1.95	1.26, 3.01	1.69	1.04, 2.76
Frail	3.66	2.12, 6.32	2.36	1.29, 4.31	2.40	1.32, 4.35
Phenotype frailty + Cumulative deficit indices						
Phenotype (Robust)	—	—	—	—	—	—
Phenotype (Pre-Frail) & Cumulative (Robust)	1.22	0.77, 1.94	1.68	1.03, 2.74	1.71	0.98, 3.00
Phenotype (Pre-Frail) & Cumulative (Pre-Frail or Frail)	2.52	1.65, 3.85	2.21	1.39, 3.53	1.67	0.96, 2.92
Phenotype (Frail)	3.79	2.20, 6.52	2.39	1.31, 4.37	2.40	1.32, 4.35
Usual gait speed (m/s)						
>=0.8	—	—	—	—	—	—
0.6 to <0.8	1.92	1.35, 2.74	1.02	0.71, 1.47	1.22	0.76, 1.97
<0.6	3.58	2.34, 5.48	1.33	0.82, 2.16	1.63	0.96, 2.75
Usual gait speed + Cumulative deficit index						
Gait speed (>=0.8)	—	—	—	—	—	—
Gait speed (0.6 to <0.8) & Cumulative (Robust)	1.21	0.74, 1.97	0.85	0.51, 1.41	1.03	0.56, 1.88
Gait speed (0.6 to <0.8) & Cumulative (Pre-Frail or Frail)	2.89	1.93, 4.34	1.16	0.76, 1.75	1.51	0.82, 2.77
Gait speed (<0.6)	3.67	2.40, 5.62	1.35	0.83, 2.18	1.63	0.97, 2.76
Usual gait speed (per 0.1 m/s decrease)	1.20	1.13, 1.27	1.06	0.98, 1.14	1.06	0.99, 1.13
During the last week, on how many days did you walk outside?						
>=3 days	—	—	—	—	—	—
<3 days	1.77	1.17, 2.67	1.56	0.98, 2.49	0.98	0.54, 1.76
Was the patient dependent on the assistance of others to complete the assessment?						
Without help	—	—	—	—	—	—
With help or unable	1.05	0.65, 1.69	1.50	0.90, 2.50	1.98	1.09, 3.59

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

Supplemental Table 5: Distribution of patients across phenotype and gait speed + cumulative deficit frailty reclassifications

	Overall N = 1011	**Lymphoma** N = 410	**Leukemia** N = 230	**Myeloma** N = 189	**Other** N = 182
Phenotypic frailty + Cumulative deficit indices					
Phenotype (Robust)	305 (30%)	123 (30%)	56 (24%)	60 (32%)	66 (36%)
Phenotype (Pre-Frail) & Cumulative (Robust)	291 (29%)	127 (31%)	61 (27%)	48 (25%)	55 (30%)
Phenotype (Pre-Frail) & Cumulative (Pre-Frail or Frail)	303 (30%)	124 (30%)	86 (37%)	50 (26%)	43 (24%)
Phenotype (Frail)	112 (11%)	36 (9%)	27 (12%)	31 (16%)	18 (10%)
Usual gait speed + Cumulative deficit index					
Gait speed (≥ 0.8)	552 (55%)	228 (56%)	125 (54%)	97 (51%)	102 (56%)
Gait speed (0.6 to < 0.8) & Cumulative (Robust)	152 (15%)	62 (15%)	28 (12%)	27 (14%)	35 (19%)
Gait speed (0.6 to < 0.8) & Cumulative (Pre-Frail or Frail)	156 (15%)	59 (14%)	49 (21%)	24 (13%)	24 (13%)
Gait speed (< 0.6)	151 (15%)	61 (15%)	28 (12%)	41 (22%)	21 (12%)

Supplemental Table 6: Kaplan-Meier estimates of median overall survival and 1- and 5-year survival probabilities, by frailty assessments.

	Median Survival	1-Year Survival	5-Year Survival
	Months (95% CI)	% (95% CI)	% (95% CI)
Cumulative deficit index			
Robust	75 (68, 85)	89% (86%, 91%)	61% (56%, 66%)
Pre-Frail	39 (28, 48)	74% (69%, 79%)	35% (30%, 42%)
Frail	26 (18, 38)	68% (59%, 78%)	21% (14%, 32%)
Phenotypic frailty index			
Robust	92 (80, NE)	90% (86%, 94%)	67% (61%, 73%)
Pre-Frail	49 (42, 56)	80% (77%, 84%)	44% (40%, 49%)
Frail	24 (18, 38)	66% (57%, 75%)	20% (13%, 31%)
Usual gait speed (m/s)			
≥ 0.8	73 (67, 81)	85% (82%, 88%)	58% (54%, 63%)
0.6 to < 0.8	49 (41, 57)	81% (76%, 85%)	41% (35%, 48%)
< 0.6	25 (18, 35)	70% (62%, 78%)	25% (18%, 34%)
Phenotypic frailty + Cumulative deficit indices			
Phenotype (Robust)	92 (80, NE)	90% (86%, 94%)	67% (61%, 73%)
Phenotype (Pre-Frail) & Cumulative (Robust)	66 (51, 73)	86% (82%, 90%)	54% (48%, 61%)
Phenotype (Pre-Frail) & Cumulative (Pre-Frail or Frail)	38 (28, 46)	75% (70%, 80%)	35% (29%, 42%)
Phenotype (Frail)	24 (18, 38)	66% (57%, 75%)	20% (13%, 31%)
Usual gait speed + Cumulative deficit index			
Gait speed (≥ 0.8)	73 (67, 81)	85% (82%, 88%)	58% (54%, 63%)
Gait speed (0.6 to < 0.8) & Cumulative (Robust)	64 (50, NE)	89% (84%, 94%)	52% (43%, 63%)
Gait speed (0.6 to < 0.8) & Cumulative (Pre-Frail or Frail)	39 (28, 50)	73% (66%, 80%)	31% (24%, 40%)
Gait speed (< 0.6)	25 (18, 35)	70% (62%, 78%)	25% (18%, 34%)

NE: Not estimable

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