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

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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: 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 5: 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

Supplemental Table 6: 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

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