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Hand grip strength and 2 minute walk test in chronic GVHD assessment: An analysis from the Chronic GVHD Consortium

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Abstract

Hand grip strength (HGS) and 2 minute walk test (2MWT) have been proposed as elements of chronic graft-vs-host disease (GVHD) assessment in clinical trials. Using all available data (n=584 enrollment visits, 1,689 follow-up visits, total of 2,273 visits) from a prospective observational cohort study, we explored the relationship between HGS and 2MWT and patient-reported measures (Lee symptom scale, SF-36 and FACT-BMT quality of life instruments, and Human Activity Profile, or HAP), chronic GVHD global severity (NIH global 0–3 score, clinician global 0–3 score, and patient-reported global 0–3 score), calculated and clinician-reported chronic GVHD response, and mortality (overall survival (OS), non-relapse mortality (NRM), and failure-free survival (FFS)) in multivariable analyses adjusted for significant covariates. 2MWT was significantly associated with intuitive domains of the Lee Symptom Scale (overall, skin, lung, energy), SF-36 domain and summary scores, FACT summary and domain scores, and HAP scores (all $p < 0.001$). Fewer associations were detected with the HGS. The 2MWT and HGS both had significant association with global chronic GVHD severity. In multivariable analysis, 2MWT was significantly associated with OS, NRM, and FFS, while no association was found for HGS. 2MWT and HGS were not sensitive to NIH or clinician-reported response. Based on independent association with mortality, these data support the importance of the 2MWT for identification of high-risk chronic GVHD patients. However, change in 2MWT is not sensitive to chronic GVHD response, limiting its usefulness in clinical trials.

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Introduction

Chronic graft-versus-host disease (GVHD) is an important source of mortality, impaired quality of life (QOL), disability and prolonged duration of immune suppression following allogeneic hematopoietic cell transplantation (HCT).[1–6] Following a National Institutes of Health (NIH) consensus conference, a series of expert opinion-based recommendations aimed to standardize diagnosis, scoring, histopathology, biomarkers, response assessment and the conduct of clinical trials in chronic GVHD.[7–12] Among the proposed measures for assessing chronic GVHD were the 2 minute walk test (2MWT) and the hand grip strength (HGS).

Measures of exercise tolerance have been utilized in multiple settings to diagnose impairment, monitor change in ability over time and with interventions, and to estimate prognosis. One of the most widely used is the 6 minute walk test,[13] which has been studied in several cardiopulmonary conditions including COPD,[14] pulmonary artery hypertension, interstitial lung disease, congestive heart failure,[15] and in cardiopulmonary rehabilitation.[16] Most studies demonstrate that this test is valid, reliable, and responsive to change. Impaired performance has been associated with mortality in the setting of COPD,[17] end-stage renal disease,[18] and congestive heart failure.[15] Walking speed has also been associated with all-cause mortality among older community dwelling adults.[19] Similarly, the 2MWT has been validated in COPD,[20] but little information exists regarding the utility of this measure following HCT.[21]

The hand grip strength (HGS) test, a measure of voluntary muscle function, has been studied as an indicator of muscle mass and nutritional status. Multiple studies have demonstrated an association between disease-related malnutrition and grip strength.[22] Impaired HGS has been associated with increased risk for post-operative complications, lower functional status, hospital re-admission rates, functional limitations and disability,[22] and overall mortality among healthy adults and older adults,[19] as well as those with chronic illness including chronic kidney disease.[23, 24] While HGS has been shown to be sensitive to decreased muscle strength early after HCT and in the setting of acute GVHD,[25] HGS has not been previously studied in the setting of chronic GVHD.

In summary, allied literature supports the 2MWT and HGS as important measures of physiologic reserve and vulnerability in both healthy adults and those with chronic medical conditions. We examined these recommended measures among chronic GVHD-affected HCT recipients to determine their association with patient-reported measures, chronic GVHD severity, chronic GVHD response, and mortality.

Methods

Chronic GVHD cohort

The Chronic GVHD Consortium has developed a multi-center observational cohort study of chronic GVHD-affected HCT recipients.[26] Included subjects are allogeneic HCT recipients age 2 or greater with chronic GVHD requiring systemic immunosuppressive therapy.[8] Cases are classified as incident (enrollment less than 3 months after chronic GVHD diagnosis) or prevalent (enrollment three or more months after chronic GVHD diagnosis but less than 3 years after transplant). Exclusion criteria include primary disease relapse, and inability to comply with study procedures.

Clinicians and patients report standardized information on chronic GVHD organ involvement and symptoms at cohort enrollment and at serial follow up visits (every six months for prevalent cases vs. at 3 months, then every 6 months for incident cases). Chronic

GVHD global severity according to the NIH Chronic GVHD Consensus is scored according to objective criteria for each organ involved, which is summarized for an overall score of mild, moderate or severe.[8] Additional measures examine the impact of chronic GVHD on functional ability, symptom burden, and QOL. The assessments performed reflect the recommendations of the NIH Consensus Conference.

Hand grip strength and 2 minute walk test

Functional measures examined in this analysis include standardized hand grip strength (HGS), and 2 minute walk test (2MWT). In the assessment of HGS, strength is measured three times from the dominant hand using a portable electronic dynamometer.[10, 27] In the conduct of the 2MWT, the patient is instructed to walk a 50 foot course (25 feet each direction) with 180 degree turns at each end, and the total distance covered in two minutes is recorded.[10, 21, 28]

Patient reported measures

The Lee Chronic GVHD Symptom Scale is a 30 item, 7 subscale symptom scale, which evaluates adverse effects of chronic GVHD on skin, vitality, lung, nutritional status, psychological functioning, eye, and mouth symptoms.[29] The Human Activity Profile (HAP) is a 94-item self-reported assessment of energy expenditure and physical fitness. The instrument was first developed in a population with pulmonary disease, and has since been validated in an HCT population.[30],[31] Respondents indicate whether they never did, have stopped or are still performing listed activities. A maximum activity score (MAS), adjusted activity score (AAS), and modified adjusted activity score are calculated. The FACT-BMT v4.0 is a 37 item self-report questionnaire, which includes a 10 item Bone Marrow Transplant Subscale (BMTS). The instrument measures the effect of cancer therapy on multiple QOL domains including physical (PWB), functional (FWB), social/family, and emotional well being, and BMT specific concerns. Individual domain scores can be summarized to give a total FACT-BMT score (including all subscales) or a FACT-TOI (PWB + FWB + BMTS).[32, 33] The SF-36 v2 is a 36 item self-report questionnaire which assesses health and functioning. The instrument examines the following domains: physical functioning (PF), role functioning-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role functioning-emotional (RE), and mental health (MH). Two summary scales from the SF-36 include the physical component score (PCS) and the mental component score (MCS).[34–37]

Statistical methods

Patient, transplantation, and chronic GVHD characteristics of the study subjects were summarized with descriptive statistics including median and range, or frequencies and percentages according to the nature of the data. All available cohort data (through 3/31/2012) from enrollment and serial follow up visits were utilized for these analyses. Grip strength data was adjusted for gender, age, and grip position, as recommended.[38]

To account for within-patient correlation, linear mixed models with random patient effects were used for continuous outcomes, and the generalized estimating equations (GEE) were utilized for binary outcomes. Considering multiple testing, Type I error was controlled by treating a two-sided p value of less than 0.01 as statistically significant.

Logistic regression models with GEE method were used to assess whether missing 2MWT or HGS data were associated with patient, disease, or transplantation characteristics.

For the analysis of symptom scale, QOL and HAP measures as outcomes, multivariable linear mixed models were constructed utilizing all visit data. The variables of 2MWT and

HGS were put in the same model, while adjusting for significant covariates, including: patient age at HCT (<50, higher), patient gender, patient education level (high school or lower, college level, graduate school level, missing), month from HCT to cohort enrollment (<12 months, higher), donor-patient gender combination (female into male, other), Karnofsky performance status (<80, 80+, missing), platelet count (<100K, higher), NIH global severity (less than mild, moderate, severe), bilirubin (≤2, higher), and overlap vs. classic chronic GVHD status.

In the analysis of 2MWT and HGS with global chronic GVHD severity, linear mixed models were used to study the association between these functional measures and three different global severity scores: NIH global 0–3 severity score, clinician-reported overall 0–3 severity score, and patient-reported overall 0–3 severity score. The association between binary individual organ sites of chronic GVHD involvement and 2MWT and HGS was also investigated using logistic regression models with GEE method. Individual organ involvement was defined by clinician report. Adjusted covariates included patient age at transplant (<50, higher), patient gender, month from HCT to cohort enrollment (<12 months, higher), donor-patient gender combination (female into male, other), Karnofsky performance status (<80, 80+, missing), Case type (incident, prevalent), platelet count (<100K, higher), study site (FHCRC, other), and overlap vs. classic chronic GVHD type.

In addition, using linear mixed models, we studied the association between change in HGS and 2MWT with chronic GVHD response (both NIH calculated response and clinician reported response categories) at 6 months from cohort enrollment. NIH organ specific (skin, eye, mouth, GI, liver, lung) and overall responses were defined by the provisional algorithms proposed at the 2005 NIH consensus conference.[10] Clinician reported response as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Change in HGS and 2MWT was studied with respect to the response categories of CR/PR vs. SD/PD, and also CR vs. PR/SD/PD.

As well, we studied the relationship between clinically meaningful change (defined as ≥ 0.5 SD change) in 2MWT and HGS and the 6 month response (in 3 categories, namely response (CR/PR), stable disease, and progression) using the gamma statistic, which measures concordance between ordinal categorical measures; this statistic ranges from −1 to 1, with value < 0.4 considered poor concordance empirically.

Finally, multivariable Cox regression was performed to study the association between 2MWT and HGS with overall survival (OS), non-relapse mortality (NRM), and failure-free survival (FFS). NRM was defined as death without prior relapse. OS was calculated from the time of enrollment, with patients censored at date last known alive. For the calculation of FFS, events included death, relapse, or utilization of additional systemic immune suppressive therapy (included as an objective measure of chronic GVHD treatment failure). Separate models were constructed to evaluate only cohort enrollment data, and then all available data in a time-varying model. In separate analyses, we explored both quartile and median cut points in the 2MWT data to determine a threshold for increased mortality. Change in 2MWT and HGS at 6 months was tested for correlation with subsequent OS and NRM. In survival analyses, covariates included: study site (FHCRC, other), case type (incident, prevalent), month from HCT to cohort enrollment (<12 months, higher), platelet count (<100K, higher), Karnofsky performance status (<80, 80+, missing), patient age at transplant (<50 vs. higher), donor match relation (matched related, matched unrelated, mismatched), donor-patient gender combination (female into male vs. other), transplant type (myeloablative vs. not), bilirubin (≤2, higher), NIH global severity (less than mild, moderate, severe), and overlap vs. classic chronic GVHD type.

Statistical analyses were performed with SAS/STAT software, version 9.3 (SAS Institute, Inc., Cary, NC) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

584 individual patients (1,689 follow-up visits, total of 2,273 visits) contributed data to the analysis. The cohort included both incident and prevalent cases and predominantly adults. Patient, disease, and transplantation characteristics are represented in Table 1. Among patient characteristics studied, those with any missing 2MWT data were more likely to have KPS < 80% ($p < 0.001$) and greater NIH global chronic GVHD severity ($p = 0.02$). Those enrolled at Fred Hutchinson Cancer Research Center (FHCRC) were less likely to have missing HGS data ($p < 0.001$). Other variables did not differ according to the presence or absence of missing 2MWT or HGS data.

Patient reported measures

In multivariable analysis adjusting for significant clinical covariates, shorter 2MWT were still associated with higher Lee Chronic GVHD Symptom Scale overall, skin, lung, and energy domains (all $p < 0.001$). Among the studied QOL measures, 2MWT were also associated with the SF-36 instrument PCS, PF, RP, GH, and VT (all $p < 0.001$), but not with MCS. Similarly, there was significant association between 2MWT and the FACT instrument FACT-G, FACT-TOI, FACT-BMT, PWB, and FWB (all $p < 0.001$). Association was also found between 2MWT and the HAP scores, including MAS, AAS, and modified AAS (all $p < 0.001$).

In contrast, fewer associations were detected in the case of the HGS: None of the Lee Chronic GVHD Symptom Scale domains met the specified $p < 0.01$ level of significance. Among the studied QOL instruments, HGS was associated with the SF-36 PCS summary score ($p = 0.002$) and GH ($p = 0.002$), as well as the FACT instrument FACT-TOI ($p = 0.002$), FACT-BMT ($p = 0.008$), and FWB ($p < 0.001$). Among HAP scores, only the AAS had significant association with HGS ($p = 0.005$).

Chronic GVHD severity and organ involvement

As presented in Table 2, the 2MWT had significant association with global severity according to NIH global score, as well as clinician and patient-reported chronic GVHD severity. Patients with NIH global score of less than mild or mild and moderate achieved on average 20.7 and 15.3 feet greater distance compared to those with NIH severe chronic GVHD. This effect was even more striking for clinician- and patient-reported global chronic GVHD severity. In addition, significant associations were detected for each in the case of HGS.

Impaired performance in the 2MWT was associated with higher odds of GI, liver, and lung involvement (Table 3). Conversely, no individual sites of chronic GVHD involvement met the $p < 0.01$ significance level in association with the HGS. As a separate approach, we also examined the relationship between 2MWT and HGS and the designation of either single organ or multiple organ site involvement with chronic GVHD. Out of 2273 total visits, the majority (n=1895) had multiple organ involvement, while less (n=365) had single organ involvement (13 missing). Univariable logistic regression models showed that greater 2MWT had lower odds of multiple organ involvement ($p=0.15$), and a similar trend was observed for the HGS ($p=0.36$), but the association was not statistically significant.

Change in HGS and 2MWT: Association with chronic GVHD response

No significant associations were detected between change in HGS or 2MWT and either the NIH calculated or clinician reported chronic GVHD response at 6 months from cohort enrolment. Similarly, no significant associations were detected when individual organ responses were studied. In our analysis of clinically meaningful change, the majority of patients had stable disease, namely no clinically meaningful improvement or worsening in 2MWT or HGS (Table 4). Both 2MWT and HGS demonstrated poor concordance with six month NIH response (both overall response and individual organ responses) and six month clinician-reported overall response (all had gamma statistic < 0.4).

Survival and non-relapse mortality

As demonstrated in Table 5, greater distance achieved in the 2MWT was significantly associated with reduced hazard for death. This conclusion held true both for both OS and NRM outcomes, and also in separate models based on enrollment data alone, or using all data in a time-varying model. Results were similar for the endpoint of FFS (failure-free survival). In subsequent analyses, we explored quartile and median cut-points in the observed 2MWT data to discern a threshold for increased mortality. Those less than the median value had significantly increased hazard for mortality, and this effect was most pronounced in the time-varying model (Table 5). Change in 2MWT or HGS after 6 months was not associated with subsequent OS or NRM.

Discussion

Valid, safe, and practical methods for assessing functional impairment and vulnerability among chronic GVHD-affected HCT patients are needed. Measures of exercise tolerance and voluntary muscle strength have proven useful in other chronic health conditions. We examined whether the 2MWT and HGS measures recommended by the NIH consensus conference were associated with patient-reported measures, chronic GVHD severity, chronic GVHD response, and mortality.

The major finding from this analysis is the independent association of the 2MWT with mortality among chronic GVHD affected HCT patients. This important effect was discerned, independent of relevant patient, disease, and transplantation covariates (including chronic GVHD global severity). Beyond this major finding, impaired 2MWT was significantly associated with higher symptom burden, impaired quality of life across multiple domains, functional disability assessed by the HAP instrument, and increased mortality. While the exact cause of impaired performance on the walk test is largely not known among chronic GVHD patients, it likely represents the combined burden of reduced cardiopulmonary fitness, impaired function in chronic GVHD target organs, decreased muscle strength, a multifactorial volitional component (as it is a self-paced test), as well as the impact of immune suppressive therapies (e.g. muscle atrophy and dependent edema related to systemic glucocorticoid therapy). Interestingly, GI, liver and lung involvement were identified as particularly important among this chronic GVHD cohort. This may reflect both direct contributions of organ involvement, as well as impact from systemic immune suppressive therapy.

We could not, however, demonstrate that change in 2MWT (including clinically meaningful change) has significant association with calculated or clinician-reported chronic GVHD response. As change in 2MWT (or HGS) is not sensitive to chronic GVHD response, these measures do not have a role in assessing response in therapeutic trials or clinical practice. As well, change in 2MWT (and HGS) did not have association with subsequent mortality,

further consolidating this finding. Rather, the 2MWT appears to be useful to describe the type of patients who enroll in a study, and to place their underlying mortality risk in context.

The data largely do not support the importance of the HGS among chronic GVHD patients. While HGS has association with some QOL summary scores, HAP-AAS, and global chronic GVHD severity, there was no significant association with mortality, and no association with chronic GVHD response. The lack of association with mortality in this cohort diverges from published data that support the HGS as predictive of overall and cause-specific mortality among healthy adults, elderly, and within certain chronic illness groups.[19, 22–24] Based on the available data in the cohort study, we can not address other important outcomes previously reported in allied literature, such as treatment complications, hospital re-admission rates, or nutritional endpoints.[22]

The large sample size of the cohort and prospectively acquired data bring strength to this analysis. However, we offer the following limitations: First, these two measures do not encompass the range of available approaches for assessing functional impairment. Alternative methods such as the 6 minute walk test or more sophisticated technology such as cardiopulmonary exercise testing may provide additional information. Interestingly, a previous analysis has shown significant correlation between HGS and a more involved measurement of isometric muscle strength in major muscle groups of the upper extremity among patients after HCT.[25] As well, integration of such functional measures and other estimates of frailty and comorbidity may enhance ability to detect those at risk. Further study is needed in this regard.

In conclusion, these data support that the 2MWT is associated with patient-reported measures, chronic GVHD severity and mortality. However, it is not sensitive to chronic GVHD response. The data do not support the ongoing use of the HGS.

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Table 1

Cohort characteristics at study enrollment (N=584)

Characteristics	Category	n	Count (%)	Median	Min	Max
Study site	Fred Hutchinson Cancer Research Center	584	254 (43%)			
	University of Minnesota		61 (10%)			
	Dana-Faber Cancer institute		65 (11%)			
	Stanford University Medical Center		73 (13%)			
	Northwest Children's Hospital		13 (2%)			
	Vanderbilt University Medical Center		47 (8%)			
	Medical College of Wisconsin		23 (4%)			
	Washington University Medical Center		4 (1%)			
	Moffitt Cancer Center		39 (7%)			
	Memorial Sloan-Kettering Cancer Center		5 (1%)			
Case type	Incident	584	346 (59%)			
	Prevalent		238 (41%)			
Adults or children	Adults	584	570 (98%)			
	Children		14 (2%)			
Patient age at cohort registration (years)		584		51.5	2	79
Patient gender	Female	584	248 (42%)			
	Male		336 (58%)			
Months from transplant to cGVHD onset		584		7.3	1.2	291
Months from cGVHD onset to enrollment		584		1.8	0	32.5
Diagnosis	AML	584	194 (33%)			
	ALL		69 (12%)			
	CML		30 (5%)			
	CLL		46 (8%)			
	MDS		88 (15%)			
	NHL		84 (14%)			
	HD		17 (3%)			
	MM		29 (5%)			

Characteristics	Category	n	Count (%)	Median	Min	Max
	AA		7 (1%)			
	Other		20 (4%)			
Disease status	Early	580	190 (33%)			
	Intermediate		247 (42%)			
	Advanced		143 (25%)			
Transplant source	Bone marrow	584	40 (7%)			
	Cord blood		28 (5%)			
	Peripheral blood		516 (88%)			
Transplant type	Myeloablative	581	334 (57%)			
	Non-myeloablative		247 (43%)			
Donor-patient CMV status	Patient and donor CMV both negative	578	195 (34%)			
	Patient or donor CMV positive		383 (66%)			
Donor-patient gender combination	Female into Male	578	168 (29%)			
	Others		410 (71%)			
Donor match	Matched related	582	243 (42%)			
	Matched unrelated		244 (42%)			
	Mismatched		95 (16%)			
Prior acute GVHD	Have prior acute GVHD	584	384 (66%)			
	No prior acute GVHD		200 (34%)			
Karnofsky performance score	80+	584	309 (53%)			
	<80		184 (31%)			
	Missing		91 (16%)			
Total serum bilirubin (mg/dL)	≤2	579	549 (95%)			
	>2		30 (5%)			
Platelet count (k/ul)	<100	581	91 (16%)			
	≥100		490 (84%)			
NIH 0–3 cGVHD global severity score	None	584	3 (1%)			
	Mild		50 (8%)			
	Moderate		304 (52%)			

Characteristics	Category	n	Count (%)	Median	Min	Max
	Severe		227 (39%)			
Clinician 0–3 cGVHD severity score	None	583	1 (<1%)			
	Mild		271 (46%)			
	Moderate		250 (43%)			
	Severe		61 (10%)			
Patient 0–3 cGVHD severity score	None	487	13 (3%)			
	Mild		251 (51%)			
	Moderate		181 (37%)			
	Severe		42 (9%)			
Walk test (feet)		492		500	170	1150
Grip strength (lb)		546		60	2	167

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; HD, Hodgkin lymphoma; MM, multiple myeloma; AA, aplastic anemia; CMV, cytomegalovirus.

Table 2

Association of 2 minute walk test and hand grip strength with chronic GVHD global severity score

Measure*	Severity	Group	n	p-value	Estimate**	95% Lower CI	95% Upper CI
2MWT	NIH	None/Mild	302	0.005	20.74	6.38	35.10
	NIH	Moderate	971	0.004	15.27	4.83	25.70
	NIH	Severe	505		0		
2MWT	Clinician	None/Mild	1089	<0.001	37.86	19.46	56.26
	Clinician	Moderate	561	0.006	25.12	7.25	43.00
	Clinician	Severe	122		0		
2MWT	Patient	None/Mild	945	<0.001	66.12	43.95	88.29
	Patient	Moderate	424	0.001	38.11	15.95	60.27
	Patient	Severe	83		0		
HGS	NIH	None/Mild	327	0.005	2.10	0.63	3.58
	NIH	Moderate	1111	<0.001	2.33	1.24	3.41
	NIH	Severe	599		0		
HGS	Clinician	None/Mild	1233	<0.001	3.80	1.96	5.63
	Clinician	Moderate	645	0.23	1.17	−0.75	3.09
	Clinician	Severe	152		0		
HGS	Patient	None/Mild	1052	<0.001	4.39	2.10	6.69
	Patient	Moderate	487	0.005	3.47	1.06	5.88
	Patient	Severe	98		0		

*2MWT = 2 minute walk test; HGS = hand grip strength

**Estimates represent additional feet (2 minute walk test) or lb (hand grip strength) achieved with reference to severe chronic GVHD group for each comparison

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Table 3

Site of chronic GVHD organ involvement – association with 2 minute walk test and hand grip strength

Measure	n	Effect*	p-value	Odds ratio **	95% Lower CI	95% Upper CI
Skin involvement	1717	2MWT	0.36	1.00	0.998	1.001
		HGS	0.02	0.99	0.981	0.998
Mouth involvement	1716	2MWT	0.96	1.00	0.999	1.001
		HGS	0.27	1.01	0.996	1.013
Eye involvement	1718	2MWT	0.58	1.00	0.999	1.001
		HGS	0.46	1.003	0.996	1.010
GI involvement ≠	1732	2MWT	<0.001	0.997	0.996	0.998
		HGS	0.06	0.992	0.983	1.000
Liver involvement ≠	1727	2MWT	<0.001	0.998	0.997	0.999
		HGS	0.74	0.999	0.992	1.006
Joint involvement	1718	2MWT	0.84	1.00	0.999	1.001
		HGS	0.20	0.994	0.985	1.003
Genital involvement	1575	2MWT	0.03	1.002	1.00	1.004
		HGS	0.07	0.986	0.97	1.001
Lung involvement	1718	2MWT	0.003	0.998	0.997	0.999
		HGS	0.41	1.004	0.995	1.013

*2MWT = 2 minute walk test; HGS = hand grip strength

**Odds ratio represents the likelihood of organ involvement (clinician-reported organ involvement on 0–3 score of > 0) in relationship to change in either 2 minute walk test or hand grip strength. For example, in the case of lung involvement: As 2 minute walk test increases by 1 foot, the odds of lung involvement decreases by 0.2% (odds ratio of 0.998).

≠Models adjusting for background variables for GI and liver were not estimable, so models without adjusting for background variables for these organs are reported

Table 4

Summary of clinically meaningful change in 2MWT and HGS from cohort enrollment to 6 months

Measure		% increase>0.5SD	% Stable	% decrease>0.5SD	Gamma
2MWT	NIH overall response	22	63	15	0.08
	NIH skin response	23	64	13	0.21
	NIH eye response	22	66	12	0.22
	NIH mouth response	25	64	11	0.04
	NIH GI response	28	58	14	0.17
	NIH liver response	24	61	15	−0.09
	Clinician reported response	22	63	15	0.01
HGS	NIH overall response	32	44	24	0.20
	NIH skin response	35	42	23	0.15
	NIH eye response	30	50	20	0.09
	NIH mouth response	35	42	23	0.009
	NIH GI response	35	36	29	0.39
	NIH liver response	30	43	27	0.19
	Clinician reported response	32	44	24	0.09

Table 5

Survival outcomes – Association of 2 minute walk test and hand grip strength with overall survival and non-relapse mortality

Outcome	Measure	p-value	HR	95% CI	
At enrollment					
OS	2MWT	0.002	0.996	0.994	0.999
	HGS	0.95	0.999	0.983	1.017
NRM	2MWT	0.003	0.996	0.993	0.999
	HGS	0.87	1.002	0.981	1.023
FFS	2MWT	0.07	0.999	0.998	1.000
	HGS	0.28	1.006	0.995	1.016
Time-varying					
OS	2MWT	<0.001	0.995	0.993	0.998
	HGS	0.63	0.994	0.969	1.019
NRM	2MWT	0.001	0.994	0.991	0.998
	HGS	0.95	0.999	0.967	1.032
FFS	2MWT	0.01	0.998	0.997	1.000
	HGS	0.76	1.002	0.991	1.013

2MWT grouped as ≤500 vs. >500					
Outcome	***Group***	***p-value***	***HR***	***95% CI***	
At enrollment					
OS	≤500	0.10	1.51	0.93	2.45
	>500		1		
NRM	≤500	0.05	1.93	1.00	3.72
	>500		1		
FFS	≤500	0.10	1.24	0.96	1.59
	>500		1		
Time-varying					
OS	≤500	0.002	2.58	1.41	4.73
	>500		1		

2MWT grouped as ≤500 vs. >500					
Outcome	***Group***	***p-value***	***HR***	***95% CI***	
NRM	≤500	0.02	2.55	1.17	5.56
	>500		1		
FFS	≤500	0.008	1.42	1.10	1.85
	>500				

*HR defines the hazard ratio for overall survival or non-relapse mortality according to increase in the functional test (2 minute walk test or hand grip strength) by one unit.

*2MWT = 2 minute walk test; HGS = hand grip strength