

Title: The Relationship between Frailty and Emotional Health in Older Patients with Advanced Cancer

Short Running Title: Frailty and Emotional Health

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ABSTRACT

Background:

Aging-related deficits which eventually manifest as frailty may be associated with poor emotional health in older patients with advanced cancer. This study aimed to examine the relationship between frailty and emotional health in this population.

Methods:

This was a secondary analysis of baseline data from a nationwide cluster randomized trial. Patients were aged ≥ 70 years with incurable stage III/IV solid tumors or lymphomas, ≥ 1 geriatric assessment (GA) domain impairment, and had completed the Geriatric Depression Scale, Generalized Anxiety Disorder-7, and Distress Thermometer. Frailty was assessed using a deficit accumulation index (DAI; range 0-1) based on GA, which did not include emotional health variables (depression and anxiety), and participants were stratified into robust, pre-frail, and frail categories. Multivariate logistic regression models examined the association of frailty with emotional health outcomes. Adjusted odds ratio (aOR) and 95% confidence intervals (CI) were reported.

Results:

Five hundred and forty-one patients were included (mean age: 77 years; 70-96). DAI ranged from 0.04 to 0.94; 27% of patients were classified as robust, 42% pre-frail, and 31% frail. Compared to robust patients, frail patients had an increased risk of screening positive for depression (aOR=12.8; 95% CI=6.1-27.0), anxiety (aOR=6.6; 95% CI=2.2-19.7), and emotional distress (aOR=4.62; 95% CI=2.9-8.3). Pre-frail compared to robust patients also had an increased risk of screening positive for depression (aOR=2.22; 95% CI=1.0-4.8) and distress (aOR=1.71; 95% CI=1.0-2.8).

Conclusion:

In older patients with advanced cancer, frailty is associated with poorer emotional health, which indicates a need for an integrated care approach to treating these patients.

Implications for Practice:

A relationship exists between frailty and poor emotional health in older adults with advanced cancer. Identifying areas of frailty can prompt screening for emotional health and guide delivery of appropriate interventions. Alternatively, attention to emotional health may also improve frailty.

INTRODUCTION

Frailty is an aging-related syndrome; defined as a state of accelerated accumulation of deficits, such that the more deficits individuals accumulate across a variety of physiological systems, the higher their level of frailty.[1] Thus, frailty elucidates some of the heterogeneity observed in older adults, where individuals of the same chronological age can have noticeably different biological ages and varied risks for adverse outcomes.[2] Using a deficit accumulation frailty model, it has been shown that about 22% of older adults; aged 65+, are classified as frail.[3] Furthermore, a diagnosis of cancer significantly increases the prevalence of frailty in older adults.[4] Older patients with cancer and frailty are at increased risk of postoperative complications, chemotherapy intolerance, disease progression and are susceptible to increased morbidity and mortality and decreased quality of life.[4-6] [7-9]

Emotional health is an important factor in overall health, and can be assessed by screening for depression (persistent feelings of sadness), anxiety (persistent and excessive worry), and distress (a state of emotional suffering). Depression and anxiety in older adults with cancer have been shown to be associated with poorer treatment outcomes, reduced ability to make treatment decisions, decreased adherence to lengthy treatments, increased hospital stays, and increased rates of suicide.[10-13] Unfortunately, depression is often under-recognized and under-treated, particularly in older patients with cancer.[14-16] In older adults with cancer, studies show that 9-15% screen positive for depression[10, 17, 18] and 20-30% experience symptoms of anxiety[19, 20] which can persist for years after the completion of cancer treatment.[21] The co-occurrence of cancer and elevated anxiety in older adults have been shown to be associated with worsened symptoms, decreased quality of life, decreased treatment adherence, increased hospital stays, and increased mortality.[22-24] Another aspect of emotional

health is psychological distress which has also been shown to be common in older adults with cancer and likewise is often under-recognized. In fact, Hurria et al. reported that 41% of older adults with cancer had significant psychological distress and that poor physical function, one of the contributing factors to of frailty, was a significant predictor of distress in these patients. [25].

Research examining the association between frailty and emotional health is limited. Studies in older adults without cancer have shown that those with depression were one to two times more likely to be classified as frail.[26-28] However, the relationship between frailty and varying aspects of emotional health in older patients with advanced cancer is not understood. In this analysis of baseline data from a large multicenter study that enrolled patients aged 70+ with advanced cancer, we investigated the prevalence of frailty, anxiety, depression, and distress. We also examined the relationships between frailty and emotional health in these patients. We hypothesized that patients with advanced cancer with the greatest degree of frailty would have the highest prevalence of depression, anxiety, and distress.

METHODS

Study Design, Setting, and Participants

We conducted a secondary analysis of baseline cross-sectional data from a national cluster randomized controlled trial evaluating the effect of a standardized geriatric assessment (GA) with GA-guided recommendations on communication between older patients with advanced and incurable solid tumors or lymphomas, their oncologists, and their caregivers (University of Rochester Cancer Center (URCC) 13070; ClinicalTrials.gov identifier NCT02107443). [29] The study was conducted within the URCC National Cancer Institute

Community Oncology Research Program (NCORP) and enrolled patients from 31 community oncology practice sites between October 2014 and April 2017.[29] In the primary study, eligible patients 1) were aged ≥ 70 , 2) had a diagnosis of stage III/IV solid tumor or lymphoma that was considered by their treating oncologists to be incurable, 3) were considering or receiving any type of cancer treatment (of any line), and 4) were found to have an impairment in at least one GA domain (excluding polypharmacy).[29] For this analysis we included all older patients with advanced cancer with available baseline data. Institutional review boards at the URCC NCORP Research Base and each of the NCORP Community Affiliates approved the study. All participants provided informed consent.

Measures

After informed consent was obtained, the following sociodemographic and clinical information was collected:[29] 1) demographic data, 2) patient-reported GA measures (Instrumental Activities of Daily Living, Activities of Daily Living, Patient Reported Karnofsky Performance Scale, Fall History, Older Americans Resources and Services (OARS) Questionnaire Comorbidity, Geriatric Depression Scale (GDS), Generalized Anxiety Disorder (GAD-7), Social Activities, OARS Medical Social Support, 3) objective GA measures (Polypharmacy, Mini Nutritional Assessment, Timed-Up-and-Go, Blessed Orientation Memory Concentration, Physician Rated), and 4) clinical information from medical charts (laboratory values of creatinine clearance, hemoglobin, albumin, and liver function tests; Table 1). [30-32]

Emotional Health

At baseline, participants completed validated measures of emotional health (depression, anxiety, and distress). Screening for depression was performed using the GDS, a self-reported

fifteen-item measure that assesses a person's level of enjoyment, interest, and social interactions. A point is given for each answer that indicates depression with a possible range of 0-15, and the validated cut-off for impairment is ≥ 5 . [33] Screening for anxiety was performed using the GAD-7, a self-reported seven-item measure with each item scored from zero (not at all) to three (nearly every day) with a possible range of 0-21, and the validated cut-off for impairment is ≥ 10 . [34] Screening for distress was performed using the distress thermometer, a self-reported measure that consists of an eleven point Likert scale ranging from zero (no distress) to ten (extreme distress), and the validated cut off for impairment is ≥ 4 . [35]

Frailty

Frailty was calculated using a Deficit Accumulation Index (DAI), following the standard procedures for creating a deficit accumulation frailty index: 1) variables were deficits associated with health status, 2) the prevalence of the deficits increases with age, 3) the deficits do not saturate too early, 4) the deficits covered a wide range of systems, and 5) at least 30-40 total deficits were used. [36] The variables used to create the DAI were obtained from self-reported and objective measures from the GA and followed the methodology for older adults with cancer as previously described, [37] without the inclusion of emotional health variables. Emotional health variables (depression and anxiety) included in the DAI developed by Cohen et al. [37] were not included in this study, because we aimed to examine the association between frailty and emotional health. Briefly, the DAI was constructed using the following 48 items: marital status, IADLs, ADLs, performance status, fall history, number of regularly taken medications, comorbidity, nutrition, level of social activity and social support, level of physical activity, and basic laboratory values (Table 1). Items were coded following the methodology used and validated in older adults with cancer by Cohen et al. [37] Binary answers were coded as zero if

the impairment or abnormal value was absent and one if the impairment or abnormal item was present. Items with a graded response were coded as zero if the condition was absent, one if the condition was intermediate, and two if the condition was the most adverse. The DAI was then calculated as the ratio of the actual deficit score to the potential deficit score, with scores ranging from zero to one with zero representing the least frail and one representing the most frail.[37] Patients were then stratified based on the DAI into robust (0-<0.2), pre-frail (0.2-<0.35), and frail (≥ 0.35) categories as has previously been described.[37]

Statistical Analyses

Descriptive statistics were used to examine sociodemographic factors, clinical information, and emotional health. Analysis of Variance (ANOVA) compared demographic, clinical, and emotional health characteristics of robust, pre-frail, and frail patients. The associations of frailty with emotional health (depression, anxiety, and distress) were first tested in bivariate analyses and further evaluated in stepwise multivariable logistic regression models. Frailty, age, sex, race, and cancer type were included in models a priori. During the stepwise selection process additional covariates were selected into the model at $p=0.16$ significance level. This value is close to the critical level (0.157) for which the stepwise procedure is asymptotically equivalent to the model selection based on minimum Akaike Information Criterion (AIC). This selection method was used in order to balance reducing the number of parameters in the model and the model's fit.[38-40] Additional covariates were selected using the stepwise selection process from: hormonal treatment, education, chemotherapy, income, and enrolled with a caregiver. Practice site was not included in any of the multivariate models because the baseline data were collected prior to the intervention.[29] Two-sided $p < 0.05$ were considered

statistically significant. All analyses were conducted with SAS v.9.4 (SAS Institute Inc., Cary, NC) and JMP Pro 15 (SAS Institute Inc., Cary, NC).

RESULTS

Patient, Clinical, and Emotional Health Characteristics

All participants (n=541) from the primary study were included in the analysis.[29] The mean age of participants was 76.6 years (range 70-96; SD=5.22 years). Fifty-one percent of participants were male, and the majority of participants were white (89.3%), received at least some college education (51.7%), and enrolled in the primary study with a caregiver (76.5%). Twenty-three percent of participants had gastrointestinal cancers and 26% had lung cancer. The majority of participants had stage IV cancers (88.7%) and received chemotherapy for their cancer (68.2%). A summary of participants' baseline sociodemographic and clinical characteristics is shown in Table 2. With regard to the emotional health variables, 22.2% screened positive for depression, 8.5% screened positive for anxiety, and 36.1% screened positive for distress (Table 2).

Other than age and gender, the remaining sociodemographic and clinical variables were comparable across patients with different frailty statuses. Frail participants were the oldest, followed by pre-frail participants, then robust participants (mean age 77.5 vs 76.2 vs 76.0 years). There were more male than female participants in both the robust (60.8% vs 39.2%) and pre-frail (51.6% vs 48.4%) categories (Table 2). Conversely, there were more female than male participants in the frail category (57.4% vs 42.6%; Table 2).

Prevalence and Distribution of Frailty, Depression, Anxiety, and Distress

Under a third (27%) of participants were classified as robust, with 42% classified as pre-frail and 31% classified as frail (Table 2). The mean score (for all participants irrespective of their frailty status) for depression was 3.09 (SD=2.74), anxiety 2.88 (SD=4.0), and distress 2.89 (SD=2.71; Figure 1, black bars). As frailty scores increased (robust vs pre-frail vs frail) there was also a significant increase in the mean scores of depression (1.68 vs 2.6 vs 4.86; $p<0.001$), anxiety (1.91 vs 2.14 vs 4.6; $p<0.001$), and distress (1.9 vs 2.68 vs 3.98; $p<0.001$; (Figure 1).

The more frail that the participants were (frail vs pre-frail vs robust), the more likely they were to screen positive for depression (43.8% vs 14.5% vs 7.6%; $p<0.001$), anxiety (16.5% vs 5.4% vs 3.5%; $p<0.001$), and distress (55.2% vs 31.4% vs 20.3%; $p<0.001$; Table 2).

Multivariable Analyses: Associations between Frailty and Depression, Anxiety, and Distress

We further examined the association of our primary independent variable of interest, the frailty status (pre-frail vs robust and frail vs robust), with depression, anxiety, and distress in the multivariable logistic regression analyses. Pre-frail participants were significantly more likely to screen positive for depression (adjusted odds ratio (aOR) = 2.22; 95% confidence interval (CI) = 1.04-4.76; $p<0.05$) and distress (aOR=1.71; 95% CI=1.03-2.84; $p<0.05$) compared to robust participants (Figure 2 and Table 2). Similarly, frail participants were more likely to screen positive for depression (aOR=12.81; 95% CI=6.08-27.02; <0.001), anxiety (aOR=6.60; 95% CI=2.21-19.66; $p<0.001$), and distress (aOR=4.62; 95%CI=2.90-8.34; $p<0.001$) compared to robust participants (Figure 2 and Table 3).

DISCUSSION

In this study we showed that as frailty increased in older patients with advanced cancer, patients' symptoms of depression and anxiety worsened and levels of distress rose. Compared to robust patients, pre-frail patients were more likely to screen positive for depression and distress, and frail patients, compared to robust patients, were more likely to screen positive for depression, anxiety, and distress.

The DAI was originally developed as a single variable that measures the effect of multisystem physiological changes resulting from aging-related deficits in various domains that is predictive of adverse health outcomes and mortality. Stratifying older adults with cancer based on the DAI using variables from the GA, is a useful approach to predict future adverse outcomes.[37] While the GA has been shown to robustly predict adverse outcomes in older adults with cancer receiving treatment, one of the major criticisms is that it is time consuming and can be difficult to conduct in busy oncology clinics. The results of our study suggest that by screening for emotional health using measures such as the GDS, GAD-7, and the distress thermometer, we might be able to identify which older adults with advanced cancer are at increased risk of being frail, and might benefit from a more comprehensive frailty screen. Furthermore, the fact that the multiple domains measured using the GA are interconnected suggests that interventions targeting emotional health may also help to improve frailty in older adults with advanced cancer.

Older adults with cancer who screen positive for depression and anxiety have worse treatment outcomes, longer hospital stays, and increased problems making treatment decisions.[10] The association between frailty and emotional health outcomes in frail older adults without cancer have been previously described.[41, 42] The results from our study demonstrating the association between frailty and increased depression in older adults with

advanced cancer are consistent with these previous findings in populations of older adults without cancer. A new study by Wang et al. has extended these findings and showed that, the co-occurrence of frailty (measured using a DAI frailty model) and depression in older adults without cancer is bi-directional.[43] Whether this bi-directionality is validated in older adults with advanced cancer is not yet known. It is worth noting that the prevalence of anxiety of 8.5% in our study is much less than has been previously reported in the literature of 20-30%. This difference may be due to the fact that different measuring instruments were used to screen for anxiety. In our study we used the GAD-7 to measure anxiety, however, many of the other studies measured anxiety using the Hospital Anxiety and Depression Scale (HADS).

A recent systematic review by Handforth et al. examining 20 studies of older patients with cancer found that increased mortality, postoperative mortality, and chemotherapy intolerance were outcomes associated with frailty.[4] Nonetheless emotional health was not discussed in this review, which emphasizes the dearth of studies that have examined the association between frailty and emotional health in older adults with cancer. Our study expands on this body of literature by describing the association between frailty and depression, anxiety, and distress in older adults with advanced cancer, and to the best of our knowledge we are the first to describe this relationship.

Studies in frail older adults without cancer have tested the effects of a variety of interventions aimed at mitigating frailty and improving health-related quality of life, physical health, and mental health outcomes.[44-47] Exercise and balance training interventions in frail older adults were found to not have an effect on mental health outcomes.[45] A study by Cohen et al. showed that a geriatric-evaluation and management model — medical decisions and interventions implemented as a result of vulnerabilities identified using the GA; such as referral

to physical therapy for patients with physical impairments —[48] to support frail older adults also improved mental health.[46] Furthermore, Monteserin et al. conducted a large randomized trial of 620 older adults (aged 74+) and showed that a GA-guided intervention led by geriatricians resulted in the reduction of frailty.[47] They also showed that having a low risk of depression at the beginning of the study predicted reduced frailty at the end of the study, suggesting that mental health interventions early in the treatment process might mitigate increased frailty throughout the treatment process.[47] These studies in addition to our current study suggest that interventions such as GA-guided recommendations and geriatric-evaluation and management models might have an effect on emotional health and thus frailty. Our study also underscores the need for a multi-disciplinary approach when treating older adults with cancer. Oncologists should consider the inclusion of geriatricians, physical therapists, and psychosocial clinicians, including social workers, psychologists, and psychiatrists, trained to deliver psychosocial interventions in an integrative approach to care in order to address the potential for depression, anxiety, and/or distress in frail older adults with advanced cancer.[49] Psychosocial interventions such as individual and group psychotherapy, relaxation and mindfulness training, and psychoeducation known to improve emotional health might in turn improve frailty in older adults with advanced cancer.[49, 50] Furthermore, psychosocial researchers should consider the need to address frailty to aid in the efficacy of interventions targeting emotional health in older adults with advanced cancer.

Our study provides further support for screening older adults with advanced cancer for emotional health. Likewise, screening for frailty may also identify older patients at increased risk for depression or psychological distress and provide a clinical opportunity to provide aging-related interventions to mitigate the progression of frailty. A recent American Society of Clinical

Oncology (ASCO) guideline recommended that all older adults (aged 65+) with cancer undergo a GA prior to the initiation of cancer treatment.[51] Performing a GA will aid oncologists in determining both the overall frailty status of older adults with cancer and will give insights into the status of their emotional health. The association between frailty and the increased risk of screening positive for depression, anxiety, and distress has numerous clinical implications and indicates two points at which oncologists could intervene. First, oncologists could provide interventions that address areas of frailty, which may influence emotional health outcomes. Such interventions include exercise, nutrition, and geriatric care models.[51, 52] Second, oncologists could screen older patients for depression, anxiety, and distress in order to coordinate mental health interventions which in turn might improve frailty.[51] These two points provide an integrative care approach by which interventions addressing either frailty or mental health may have indirect effects on each another in this population of older adults with cancer.

Further research is needed to identify interventions that will most effectively address frailty in older patients with advanced cancer who also have poor emotional health outcomes. Future studies should build upon these findings to identify specific pathways between frailty and depression, anxiety, and distress. While mechanisms that relate mental health to frailty remain unclear, there are numerous areas that future studies should consider. For example, frail older patients may be limited in their ability to participate in social activities, hobbies of interest, or other meaningful activities, which may in turn contribute to isolation and feelings of sadness or depression. Alternatively, an older patient predisposed to mental health related symptoms, such as depression or anxiety, might be less inclined to engage in physical activities outside of their home, whether walking with a friend or groups that support physical activity. These older adults may be at risk for frailty as they undergo treatment. It may be that such a relationship between

emotional health and frailty then becomes a negative reinforcing cycle in that the more frail a patient becomes, the greater the effect on mental health, the less likely patients may be to engage in activities that reduce frailty, and thus worsened mental health. Understanding these pathways or cycles would provide a foundation for refining and adapting both mental health and frailty interventions, and perhaps combining interventions that might specifically be applied to older patients with advanced cancer at increased risk of frailty.

The limitations of our study include the use of a cross-sectional design; thus frailty was measured and depression, anxiety, and distress were screened for at only a single time point. It is important to note that causality could not be determined and our results demonstrate the correlation of frailty and emotional health in older adults with advanced cancer. Moreover, since causality cannot be determined, it is possible that emotional health can have effects on the social activities, memory, and cognition components included in the DAI and future longitudinal studies are needed to examine this possibility. It is also important to note that in this study we only screened for depression and did not collect information on whether patients had a history of depression or if they were currently being treated for depression. In addition, the sample was predominantly white, with other races underrepresented. Future studies examining the relationship between frailty and emotional health should aim to improve accrual of those patients who are underrepresented in research. Our study had several strengths including the large sample size of older patients with advanced cancer and their recruitment from community oncology settings around the United States that typically treat the majority of patients with cancer.

CONCLUSION

Overall, the association between frailty and poor emotional health indicates a need for an integrated care approach to treating older patients with cancer. Including mental health in screening, assessing, and coordinating health care could have implications for mitigating the progression of frailty and improving the overall quality of life for these individuals. Furthermore, this study also suggests that screening for frailty can identify patients at greater risk of poor emotional health. Oncologists should consider a multi-disciplinary approach when treating older adults with cancer with the inclusion of geriatricians, physical therapists, and psychosocial clinicians who can aid in the implementation of interventions that will ultimately improve emotional health and as a consequence also frailty in older adults with advanced cancer.

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FIGURE LEGENDS:

Figure 1: Distribution of the mean scores for depression, anxiety, and distress for all patients irrespective of frailty status (black bar), robust (yellow bar), pre-frail (green bar), and frail (blue bar) older patients with advanced cancer. The x-axis shows the mean score for depression (determined using the GDS), anxiety (determined using the GAD-7), and distress (determined using the distress thermometer). ANOVA was used to compare either depression, anxiety, or distress of robust, pre-frail, and frail patients

Figure 2: Multivariable logistic regression to examine the association between frailty status and depression (A), anxiety (B), and distress (C) in pre-frail compared to robust (blue) and frail compared to robust (green) older adults with advanced cancer. Note: Besides age, sex, race, and cancer type, the following covariates were also included in the multivariate models if they had a P value of <0.16 in the stepwise models: hormonal treatment, education, chemotherapy, income, and whether the patient enrolled with a caregiver.

Table 1: Development of the Deficit Accumulation Index (DAI)

Item #	Form	Item	Frailty Risk		
			Absent (0)	Intermediate (1)	Most Adverse (2)
1	Demographics	Marital Status	Married	<ul style="list-style-type: none"> ▪ Single, Never Married ▪ Separated ▪ Domestic Partnership ▪ Widowed ▪ Divorced 	—
2	IADL	Telephone	Without Help	Need at least some help	Completely unable to
3		Travel	Without Help	Need at least some help	Completely unable to
4		Shopping	Without Help	Need at least some help	Completely unable to
5		Prepare meals	Without Help	Need at least some help	Completely unable to
6		Housework	Without Help	Need at least some help	Completely unable to
7		Take medicines	Without Help	Need at least some help	Completely unable to
8		Handle money	Without Help	Need at least some help	Completely unable to
9		ADL	Difficulty with bathing/showering	No	Yes
10	Difficulty with dressing		No	Yes	—
11	Difficulty with eating		No	Yes	—
12	Difficulty with getting out of bed or chairs		No	Yes	—
13	Difficulty with walking		No	Yes	—
14	Difficulty with using the toilet		No	Yes	—
15	Karnofsky Self-Reported Performance	Self-reported performance	<ul style="list-style-type: none"> ▪ No symptoms ▪ Minor symptoms (KPS, 100-90) 	<ul style="list-style-type: none"> ▪ Some symptoms (KPS, 80) 	<ul style="list-style-type: none"> ▪ Unable ▪ Occasional assistance ▪ Considerable assistance ▪ Disabled ▪ Severely disabled (KPS≤70)
16	Fall History	Number of falls	0-1	≥2	
17	Geriatric Assessment score guide	Scored impaired in polypharmacy (>5 regularly taken prescription medications or ≥1 high risk medications)[29]	no	yes	
18	OARS Comorbidity	Other cancer/leukemia	No	Yes	A Great Deal
19		Arthritis	No	Yes	A Great Deal
20		Glaucoma	No	Yes	A Great Deal
21		Emphysema	No	Yes	A Great Deal
22		High blood pressure	No	Yes	A Great Deal
23		Heart disease	No	Yes	A Great Deal
24		Circulation trouble	No	Yes	A Great Deal
25		Diabetes	No	Yes	A Great Deal
26		Stomach/Gastro Intestinal	No	Yes	A Great Deal
27		Osteoporosis	No	Yes	A Great Deal
28		Liver/kidney	No	Yes	A Great Deal

29		Stroke	No	Yes	A Great Deal
30		Depression	No	Yes	A Great Deal
31		Eyesight	Excellent, Good	Fair, poor, blind	A Great Deal
32		Hearing	Excellent, Good	Fair, poor, blind	A Great Deal
33	MNA	Weight loss >10%	No	Yes	—
34	Social Activities	Social activity	<ul style="list-style-type: none"> ▪ None of the time 	<ul style="list-style-type: none"> ▪ Most of the time ▪ Some of the time ▪ A little of the time 	<ul style="list-style-type: none"> ▪ All of the time
35		Change in the last 6 months	<ul style="list-style-type: none"> ▪ About as active ▪ Somewhat more active ▪ Much more active 	<ul style="list-style-type: none"> ▪ Somewhat less active ▪ Much less active 	—
36		Comparison of social activity to other their age	<ul style="list-style-type: none"> ▪ Same limited as others ▪ Less limited than others ▪ Much less limited than others 	<ul style="list-style-type: none"> ▪ Somewhat more limited ▪ Much more limited 	—
37	OARS Medical Social Support	Confined to bed	<ul style="list-style-type: none"> ▪ All of the Time ▪ Most of the time 	<ul style="list-style-type: none"> ▪ Some of the time ▪ A little of the time 	<ul style="list-style-type: none"> ▪ None of the time
38		Take to doctor	<ul style="list-style-type: none"> ▪ All of the Time ▪ Most of the time 	<ul style="list-style-type: none"> ▪ Some of the time ▪ A little of the time 	<ul style="list-style-type: none"> ▪ None of the time
39		Prepare Meals	<ul style="list-style-type: none"> ▪ All of the Time ▪ Most of the time 	<ul style="list-style-type: none"> ▪ Some of the time ▪ A little of the time 	<ul style="list-style-type: none"> ▪ None of the time
40		Daily chores	<ul style="list-style-type: none"> ▪ All of the Time ▪ Most of the time 	<ul style="list-style-type: none"> ▪ Some of the time ▪ A little of the time 	<ul style="list-style-type: none"> ▪ None of the time
41	Physician rated KPS	Karnofsky Performance Scale (KPS)	90-100	80	0-70
42	Timed “up and go”	Time taken to complete assessment	<13 secs	≥13 secs	—
43	BOMC	Cognition and Memory	<11	≥11	—
44	MNA	Body Mass Index	18.50 - 24.99	<18.5 or ≥25	—
45	Labs	Creatinine clearance	≥60	30-59	<30
46		Hemoglobin	<ul style="list-style-type: none"> ▪ Male ≥13 ▪ Female ≥12 	<ul style="list-style-type: none"> ▪ Male <13 ▪ Female <12 	—
47		Albumin	≥3.5	<3.5	—
48		Liver Function test	Normal	Abnormal	—

Note: * GDS and GAD-7 that were in the original DAI were removed in the development of the Adjusted DAI Score.

Abbreviations: Instrumental Activities of Daily Living (IADL); Activities of Daily Living (ADL); Karnofsky Performance Scale (KPS); Older Americans Resources and Services (OARS); Mini Nutritional Assessment (MNA); Geriatric Depression Scale (GDS); Generalized Anxiety Disorder-7 (GAD-7); Blessed Orientation Memory and Concentration (BOMC); Body Mass Index (BMI)

Table 2. Baseline Demographic and Clinical Characteristics

Variables	All Participants N=541 (100%)	Frailty Status (DAI)			P-value
		Robust N=143 (26.4%)	Pre-Frail N=221(40.9%)	Frail N=176 (32.5%)	
Age, years: N(%)					
Mean [Range]	76.6 [70-96]	76.0 [70-93]	76.2 [70-92]	77.5 [70-96]	0.02
70-79	401 (74.3)	110 (76.9)	168 (76.0)	123 (69.9)	
80-89	127 (23.5)	30 (23.6)	48 (21.7)	49 (27.8)	0.59
≥90	12 (2.2)	3 (2.1)	5 (2.3)	4 (2.3)	
Gender: N(%)					
Male	276 (51.1)	87 (60.8)	114 (51.6)	75 (42.6)	0.005
Female	264 (48.9)	56 (39.2)	107 (48.4)	101 (57.4)	
Race: N(%)					
White	482 (89.3)	131 (91.6)	198 (89.6)	153 (86.9)	0.40
Non-white	58 (10.7)	12 (9.0)	23 (10.4)	23 (13.1)	
Education: N(%)					
<High School	66 (12.2)	14 (9.8)	25 (11.3)	27 (15.3)	0.24
High school graduate	195 (36.1)	45 (31.5)	85 (38.5)	65 (36.9)	
Some college or above	279 (51.7)	84 (58.7)	111 (50.2)	84 (47.7)	
Income: N(%)					
≤\$50000	265 (49.3)	65 (45.8)	110 (49.8)	90 (51.4)	0.59
>\$50000 or decline to answer	273 (50.7)	77 (54.23)	111 (50.2)	85 (48.6)	
Cancer Type: N(%)					
Gastrointestinal	138 (22.6)	30 (20.8)	68 (30.8)	40 (22.8)	0.47
Lung	140 (25.9)	32 (22.2)	54 (24.4)	54 (30.9)	
Other	262 (48.5)	82 (56.9)	99 (44.8)	81 (46.3)	
Cancer Stage: N(%)					
III	47 (8.7)	14 (9.7)	19 (8.6)	14 (8.0)	0.98
IV	480 (88.7)	127 (88.2)	196 (88.7)	157 (89.7)	
Other	13 (2.4)	3 (2.1)	6 (2.7)	4 (2.3)	
Chemotherapy (%)					
Chemotherapy	369(68.2)	89 (62.2)	160 (72.4)	120 (68.6)	0.13
No	172 (31.8)	54 (37.8)	61 (27.6)	55 (31.4)	
Hormonal Treatment (%)					
Hormonal	97 (18.0)	33 (22.9)	40 (18.1)	24 (13.7)	0.10
No	443 (82.0)	111 (77.1)	181 (81.9)	151 (86.3)	
Enrolled with a Caregiver: N(%)					
Yes	414 (76.5)	109 (75.7)	168 (76.0)	137 (77.8)	0.88
No	127 (23.4)	35 (24.3)	53 (24.0)	39 (22.2)	
Depression (GDS)					
Yes (≥5)	120 (22.2)	11 (7.6)	32 (14.5)	77 (43.8)	<0.001
No (<5)	421 (77.8)	133 (92.4)	189 (85.5)	99 (56.2)	
Anxiety (GAD-7)					
Yes (≥10)	46 (8.5)	5 (3.5)	12 (5.4)	29 (16.5)	<0.001
No (<10)	495 (91.5)	139 (96.5)	209 (94.6)	147 (83.5)	
Distress^a					
Yes (≥4)	193 (36.1)	29 (20.3)	69 (31.4)	95 (55.2)	<0.001
No (<4)	342 (63.9)	114 (79.7)	151 (68.6)	77 (44.8)	

Note: 1 participant did not provide any demographic data

Abbreviations: Geriatric Depression Scale (GDS); Generalized Anxiety Disorder-7 (GAD-7)

^aSome participants did not complete this assessment

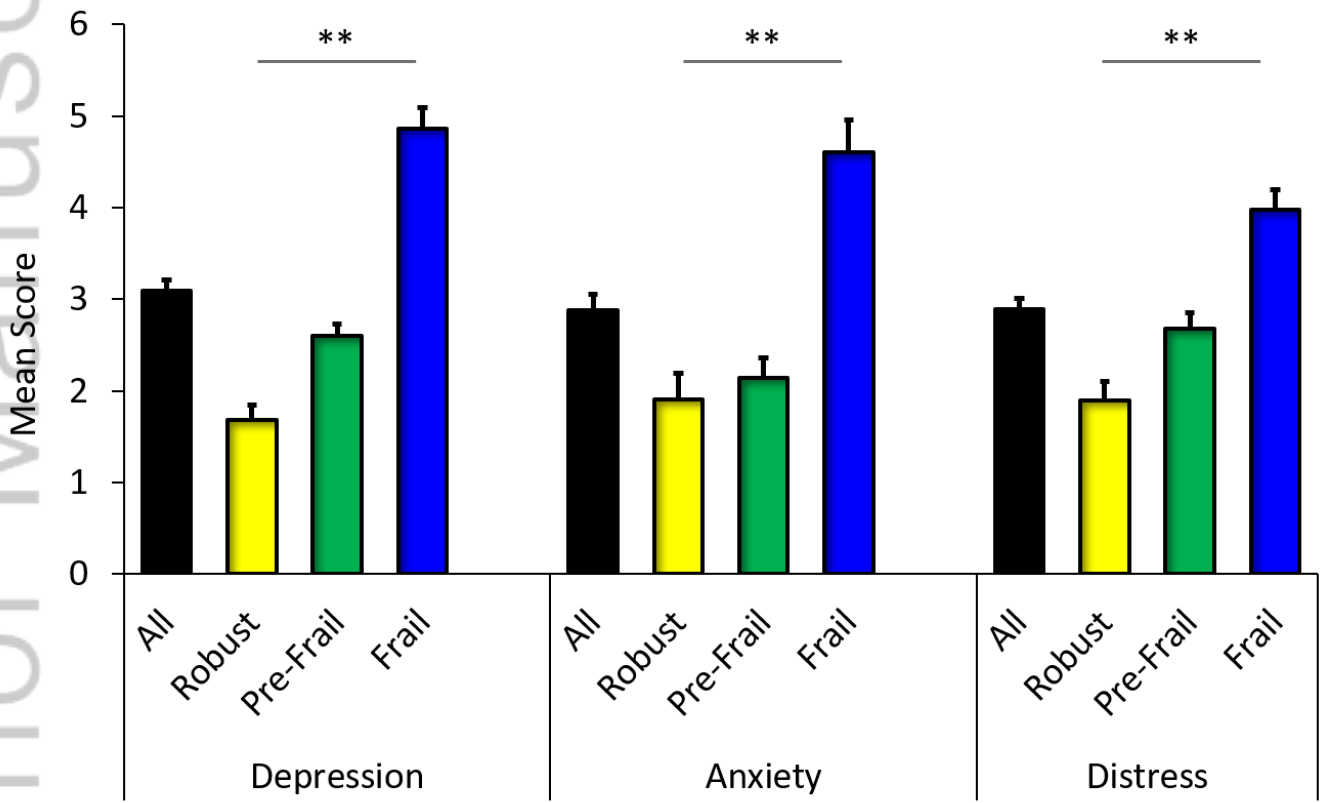
Table 3: Association of Frailty with Emotional Health Outcomes in Models Adjusting for Baseline Demographic and Clinical Predictors

	Depression (GDS \geq5)	Anxiety (GAD-7 \geq10)	Distress (\geq4)
	Adjusted DAI OR (95% CI)	Adjusted DAI OR (95% CI)	Adjusted DAI OR (95% CI)
DAI			
Pre-Frail vs Robust	2.22 (1.04-4.76)*	1.93 (0.6-6.20)	1.71 (1.03-2.84)*
Frail vs Robust	12.81 (6.08-27.02)***	6.60 (2.21-19.66)***	4.62 (2.90-8.34)***
Age	0.95 (0.90-0.99)	0.96 (0.90-1.03)	0.97 (0.94-1.01)
Gender			
Female vs Male	1.44 (0.89-2.33)	1.07 (0.56-2.05)	0.95 (0.65-1.38)
White			
White vs Non-White	0.93 (0.44-1.97)	1.00 (0.36-2.83)	1.41 (0.74-2.68)
Cancer Type			
GI vs Other	0.52 (0.28-0.96)*	0.60 (0.25-1.42)	1.06 (0.66-1.71)
Lung vs Other	0.92 (0.54-1.60)	0.81 (0.38-1.71)	1.38 (0.87-2.18)
Hormonal Treatment			
Yes vs No	-	0.17 (0.04-0.77)*	-
Education			
High School vs <High School	1.23 (0.60-2.54)	0.70 (0.29-1.68)	-
> High School vs < High School	0.69 (0.34-1.42)	0.36 (0.15-0.88)*	-
Chemotherapy			
Yes vs No	2.12 (1.22-3.69)**	-	1.713 (1.10-2.67)*
Income			
>\$50000 or declined to answer vs \leq \$50000	1.60 (0.99-2.57)	-	-
Caregiver			
Yes or No	1.77 (0.97-3.25)	-	-

*p<0.05, **p<0.01, ***p<0.001

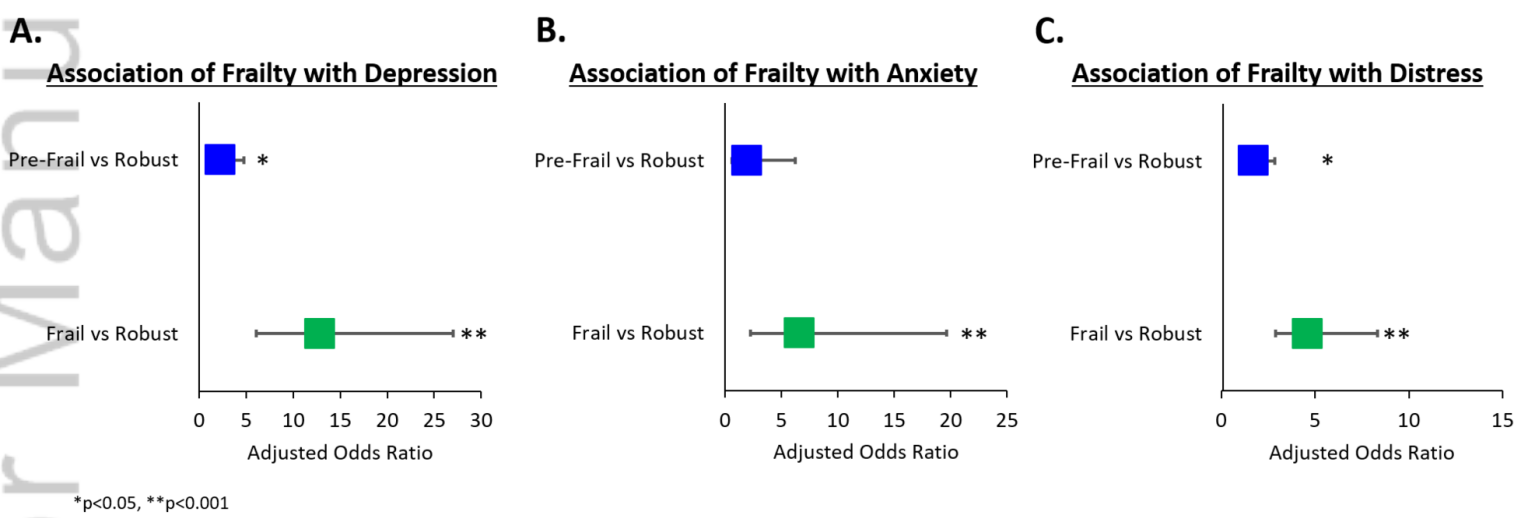
Abbreviations: Deficit Accumulation Index (DAI); Geriatric Depression Scale (GDS); Generalized Anxiety Disorder-7 (GAD-7)

Distribution of Mean Depression, Anxiety, and Distress Scores by Frailty Status (Adjusted DAI)



**p<0.001

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