The Oncologist®

Geriatric Oncology

The Relationship Between Frailty and Emotional Health in Older Patients with Advanced Cancer

Nikesha Gilmore,[a] Lee Kehoe,[a] Jessica Bauer,[a] Huiwen Xu,[a] Bianca Hall,[a] Megan Wells,[a] Lianlian Lei,[b] Eva Culakova,[a] Marie Flannery,[a] Valerie Aarne Grossman,[a,c] Ronak Amir Sardari,[a] Himal Subramanya,[a] Sindhuja Kadambi,[a] Elizabeth Belcher,[a] Jared Kettinger,[d] Mark A. O'Rourke,[e] Elie G. Dib,[f] Nicholas J. Vogelzang,[g] William Dale,[h] Supriya Mohile[a]

[a]University of Rochester Medical Center, Rochester, New York, USA; [b]University of Michigan, Ann Arbor, Michigan, USA; [c]SCOREboard Stakeholder Advisory Group, University of Rochester Medical Center, Rochester, New York, USA; [d]Grove City College, Grove City, Pennsylvania, USA; [e]Cancer Centers of the Carolinas, Greenville, South Carolina, USA; [f]Michigan Cancer Research Consortium, Ypsilanti, Michigan, USA; [g]Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada, USA; [h]City of Hope National Medical Center, Duarte, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Frailty • Emotional health • Geriatric assessment • Depression • Anxiety • Distress

Abstract

Background. Aging-related deficits that 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, had ≥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, prefrail, and frail categories. Multivariate logistic regression models examined the association of frailty with emotional health outcomes. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were reported.

Results. Five hundred 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% prefrail, and 31% frail. Compared with 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). Prefrail compared with 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. ***The Oncologist*** 2021;26:e2181–e2191

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 that is 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,

Correspondence: Supriya G. Mohile, M.D., Wilmot Cancer Institute, 601 Elmwood Avenue., Box 704, Rochester, New York 14642, USA. Telephone: 585-275-5823; e-mail: supriya_mohile@urmc.rochester.edu; or Nikesha Gilmore, Ph.D., University of Rochester Medical Center, Department of Surgery, Division of Supportive Care in Cancer, 265 Crittenden Boulevard, Box 658, Rochester, New York 14642, USA. Telephone: 585-275-1275; e-mail: nikesha_gilmore@urmc.rochester.edu Received February 16, 2021; accepted for publication August 24, 2021; published Online First on September 19, 2021. http://dx.doi.org/10.1002/onco.13975

No part of this article may be reproduced, stored, or transmitted in any form or for any means without the prior permission in writing from the copyright holder. For information on purchasing reprints contact commercialreprints@wiley.com. For permission information contact permissions@wiley.com.

© 2021 AlphaMed Press.

1549490x, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

frailty elucidates some of the heterogeneity observed in older adults, in which 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, and disease progression and are susceptible to increased morbidity and mortality and decreased quality of life [4–9].

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 undertreated, 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 has 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.

Materials and 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 (a) were aged ≥70, (b) had a diagnosis of stage III/IV solid tumor or lymphoma that was considered by their treating oncologists to be incurable, (c) were considering or receiving any type of cancer treatment (of any line), and (d) 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]: (a) demographic data, (b) patient-reported GA measures (Instrumental Activities of Daily Living [IADL], Activities of Daily Living [ADL], Patient Reported Karnofsky Performance Scale, Fall History, Older Americans Resources and Services [OARS] Questionnaire Comorbidity, Geriatric Depression Scale [GDS], Generalized Anxiety Disorder-7 [GAD-7], Social Activities, and OARS Medical Social Support), (c) objective GA measures (Polypharmacy, Mini Nutritional Assessment, Timed-Up-and-Go, Blessed Orientation Memory Concentration, Physician Rated), and (d) 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 15-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 cutoff 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 cutoff for impairment is ≥10 [34]. Screening for distress was performed using the distress thermometer, a self-reported measure that consists of an 11-point Likert scale ranging from 0 (no distress) to 10 (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: (a) variables were deficits associated with health status, (b) the prevalence of the deficits increases with age, (c) the deficits do not saturate

© 2021 AlphaMed Press.

15494908, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. Development of the DAI

Item no.	Form	Item	Frailty risk		
			Absent (0)	Intermediate (1)	Most adverse (2)
1	Demographics	Marital status	Married	• 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	• No symptoms • Minor symptoms(KPS, 100–90)	• Some symptoms (KPS, 80)	• 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

(continued)

www.TheOncologist.com

© 2021 AlphaMed Press.

15494904, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. (continued)

Item no.	Form	Item	Frailty risk		
			Absent (0)	Intermediate (1)	Most adverse (2)
25		Diabetes	No	Yes	A great deal
26		Stomach/gastrointestinal	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	• None of the time	• Most of the time • Some of the time • A little of the time	• All of the time
35		Change in the last 6 months	• About as active • Somewhat more active • Much more active	• Somewhat less active • Much less active	—
36		Comparison of social activity with others their age	• Same limited as others • Less limited than others • Much less limited than others	• Somewhat more limited • Much more limited	—
37	OARS medical social support	Confined to bed	• All of the time • Most of the time	• Some of the time • A little of the time	• None of the time
38		Take to doctor	• All of the time • Most of the time	• Some of the time • A little of the time	• None of the time
39		Prepare meals	• All of the time • Most of the time	• Some of the time • A little of the time	• None of the time
40		Daily chores	• All of the Time • Most of the time	• Some of the time • A little of the time	• None of the time
41	Physician-rated KPS	KPS	90–100	80	0–70
42	Timed "up and go"	Time taken to complete assessment	<13 seconds	≥13 seconds	—
43	BOMC	Cognition and memory	<11	≥11	—
44	MNA	BMI	18.50–24.99	<18.5 or ≥ 25	—
45	Labs	Creatinine clearance	≥60	30–59	<30
46		Hemoglobin	• Male ≥13 • Female ≥12	• Male <13 • Female <12	—
47		Albumin	≥3.5	<3.5	—
48		Liver function test	Normal	Abnormal	—

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

Abbreviations: —, not applicable; ADL, Activities of Daily Living; BMI, body mass index; BOMC, Blessed Orientation Memory and Concentration; DAI, Deficit Accumulation Index; GAD-7, Generalized Anxiety Disorder-7; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; KPS, Karnofsky Performance Scale; MNA, Mini Nutritional Assessment; OARS, Older Americans Resources and Services.

© 2021 AlphaMed Press.

15494904, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

too early, (d) the deficits covered a wide range of systems, and (e) 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, IADL, ADL, 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 to <0.2), prefrail (0.2 to <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 compared demographic, clinical, and emotional health characteristics of robust, prefrail, 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 $p = .16$ significance level. This value is close to the critical level (.157) for which the stepwise procedure is asymptotically equivalent to the model selection based on minimum Akaike Information Criterion. 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 $p < .05$ 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 prefrail 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 prefrail (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

Less than one third (27%) of participants were classified as robust, with 42% classified as prefrail 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; Fig. 1, black bars). As frailty scores increased (robust vs. prefrail vs. frail), there was also a significant increase in the mean scores of depression (1.68 vs. 2.6 vs. 4.86; $p < .001$), anxiety (1.91 vs. 2.14 vs. 4.6; $p < .001$), and distress (1.9 vs. 2.68 vs. 3.98; $p < .001$; Fig. 1).

The more frail that the participants were (frail vs. prefrail vs. robust), the more likely they were to screen positive for depression (43.8% vs. 14.5% vs. 7.6%; $p < .001$), anxiety (16.5% vs. 5.4% vs. 3.5%; $p < .001$), and distress (55.2% vs. 31.4% vs. 20.3%; $p < .001$; 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 (prefrail vs. robust and frail vs. robust), with depression, anxiety, and distress in the multivariable logistic regression analyses. Prefrail participants were significantly more likely to screen positive for depression (adjusted odds ratio [aOR] = 2.22; 95% confidence interval (CI) = 1.04–4.76; $p < .05$) and distress (aOR = 1.71; 95% CI = 1.03–2.84; $p < .05$) compared with robust participants (Fig. 2; Table 2). Similarly, frail

© 2021 AlphaMed Press.

15494490, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2. Baseline demographic and clinical characteristics

Variables	All participants $n = 541$ (100%)	Frailty status (DAI)			p value
		Robust $n = 143$ (26.4%)	Prefrail $n = 221$ (40.9%)	Frail $n = 176$ (32.5%)	
Age, yr					
Mean [range]	76.6 [70–96]	76.0 [70–93]	76.2 [70–92]	77.5 [70–96]	.02
70–79	401 (74.3)	110 (76.9)	168 (76.0)	123 (69.9)	.59
80–89	127 (23.5)	30 (23.6)	48 (21.7)	49 (27.8)	
≥90	12 (2.2)	3 (2.1)	5 (2.3)	4 (2.3)	
Gender					
Male	276 (51.1)	87 (60.8)	114 (51.6)	75 (42.6)	.005
Female	264 (48.9)	56 (39.2)	107 (48.4)	101 (57.4)	
Race					
White	482 (89.3)	131 (91.6)	198 (89.6)	153 (86.9)	.40
Non-White	58 (10.7)	12 (9.0)	23 (10.4)	23 (13.1)	
Education					
Less than high school	66 (12.2)	14 (9.8)	25 (11.3)	27 (15.3)	.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					
≤$50,000	265 (49.3)	65 (45.8)	110 (49.8)	90 (51.4)	.59
>$50,000 or decline to answer	273 (50.7)	77 (54.23)	111 (50.2)	85 (48.6)	
Cancer type					
Gastrointestinal	138 (22.6)	30 (20.8)	68 (30.8)	40 (22.8)	.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					
III	47 (8.7)	14 (9.7)	19 (8.6)	14 (8.0)	.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)	.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)	.10
No	443 (82.0)	111 (77.1)	181 (81.9)	151 (86.3)	
Enrolled with a caregiver					
Yes	414 (76.5)	109 (75.7)	168 (76.0)	137 (77.8)	.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)	<.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)	<.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)	<.001
No (<4)	342 (63.9)	114 (79.7)	151 (68.6)	77 (44.8)	

Data are shown as *n* (%) unless otherwise noted.
One participant did not provide any demographic data.
[a]Some participants did not complete this assessment.
Abbreviations: DAI, Deficit Accumulation Index; GAD-7, Generalized Anxiety Disorder-7; GDS, Geriatric Depression Scale.

© 2021 AlphaMed Press.

15494490, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

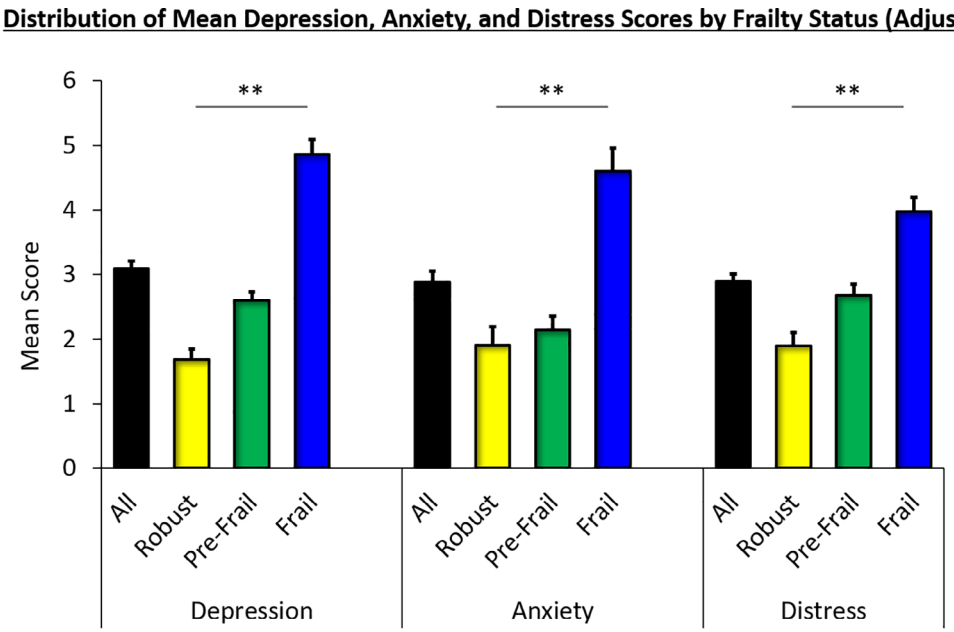


Figure 1. Distribution of the mean scores for depression, anxiety, and distress for all patients irrespective of frailty status (black bar), robust (yellow bar), prefrail (green bar), and frail (blue bar) older patients with advanced cancer. The *x*-axis shows the mean score for depression (determined using the Geriatric Depression Scale), anxiety (determined using the Generalized Anxiety Disorder-7), and distress (determined using the distress thermometer). Analysis of variance was used to compare depression, anxiety, or distress of robust, prefrail, and frail patients.

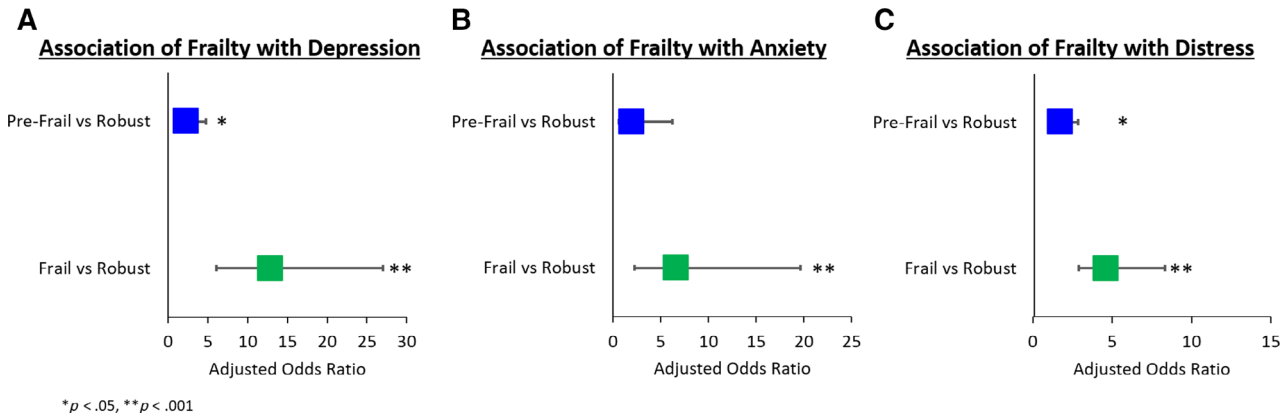


Figure 2. Multivariable logistic regression to examine the association between frailty status and depression **(A)**, anxiety **(B)**, and distress **(C)** in prefrail compared with robust (blue) and frail compared with robust (green) older adults with advanced cancer.
Note: Besides age, sex, race, and cancer type, the following covariates were also included in the multivariate models if they had a *p* value of <.16 in the stepwise models: hormonal treatment, education, chemotherapy, income, and whether the patient enrolled with a caregiver.

participants were more likely to screen positive for depression (aOR = 12.81; 95% CI = 6.08–27.02; $p < .001$), anxiety (aOR = 6.60; 95% CI = 2.21–19.66; $p < .001$), and distress (aOR = 4.62; 95% CI = 2.90–8.34; $p < .001$) compared with robust participants (Fig. 2; 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 with robust patients, prefrail patients were more likely to screen positive for depression and distress, and frail patients, compared with 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]. Although the GA has been shown to robustly predict adverse outcomes in older

© 2021 AlphaMed Press.

15494490, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

15494908, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3. Association of frailty with emotional health outcomes in models adjusting for baseline demographic and clinical predictors

	Depression (GDS ≥ 5) Adjusted DAI OR (95% CI)	Anxiety (GAD-7 ≥ 10) Adjusted DAI OR (95% CI)	Distress (≥4) Adjusted DAI OR (95% CI)
DAI			
Prefrail vs. robust	2.22 (1.04–4.76)[a]	1.93 (0.6–6.20)	1.71 (1.03–2.84)[a]
Frail vs. robust	12.81 (6.08–27.02)[b]	6.60 (2.21–19.66)[b]	4.62 (2.90–8.34)[b]
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)[a]	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)[a]	—
Education			
High school vs. less than high school	1.23 (0.60–2.54)	0.70 (0.29–1.68)	—
Greater than high school vs. less than high school	0.69 (0.34–1.42)	0.36 (0.15–0.88)[a]	—
Chemotherapy			
Yes vs. no	2.12 (1.22–3.69)[c]	—	1.713 (1.10–2.67)[a]
Income			
>$50,000 or declined to answer vs. ≤$50,000	1.60 (0.99–2.57)	—	—
Caregiver			
Yes vs. no	1.77 (0.97–3.25)	—	—

[a]$p < .05$.
[b]$p < .001$.
[c]$p < .01$.
Abbreviations: —, not applicable; CI, confidence interval; DAI, Deficit Accumulation Index; GAD-7, Generalized Anxiety Disorder-7; GDS, Geriatric Depression Scale; GI, gastrointestinal; OR, odds ratio.

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 bidirectional [43]. Whether this bidirectionality 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.

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

© 2021 AlphaMed Press.

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 multidisciplinary 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 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 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 that 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 other 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. Although 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 and the less likely patients may be to engage in activities that reduce frailty, thus leading to 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, because 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 of if they were currently being treated for depression. In addition, the sample was predominantly White, with other races under-represented. Future studies examining the relationship between frailty and emotional health should aim to improve accrual of those patients who are under-represented in research. Our study had several strengths including the large sample size of older patients with advanced cancer and their recruitment from

© 2021 AlphaMed Press.

15494490, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

community oncology settings around the U.S. 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 multidisciplinary 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, frailty in older adults with advanced cancer.

Acknowledgments

We thank Dr. Susan Rosenthal for her editorial assistance. We also thank all the SCOREboard members for their valuable contributions that resulted in the profound success of the COACH trial. This work was funded through a Patient-Centered Outcomes Research Institute (PCORI) Program contract (4634), the National Cancer Institute at the National Institutes of Health (R33 AG059206-01, UG1 CA189961, R01 CA177592, and K24 AG056589), and the University of Rochester CTSA award No. KL2TR001999. All statements in this report, including its findings and conclusions, are solely those of the authors, do not necessarily represent the official views of the funding agencies, and do not necessarily represent the views of the PCORI, its Board of Governors, or Methodology Committee. These data were presented at the Multinational Association of Supportive Care in Cancer Annual conference in 2019 as an oral presentation.

Author Contributions

Conception/design: Nikesha Gilmore, Marie Flannery, William Dale, Supriya Mohile

Provision of study material or patients: Mark A. O'Rourke, Elie G. Dib, Nicholas J. Vogelzang

Collection and/or assembly of data: Jessica Bauer, Huiwen Xu, Megan Wells, Lianlian Lei, Eva Culakova

Data analysis and interpretation: Nikesha Gilmore, Lee Kehoe, Huiwen Xu, Lianlian Lei, Eva Culakova

Manuscript writing: Nikesha Gilmore, Lee Kehoe, Jessica Bauer

Final approval of manuscript: Nikesha Gilmore, Lee Kehoe, Jessica Bauer, Huiwen Xu, Bianca Hall, Megan Wells, Lianlian Lei, Eva Culakova, Marie Flannery, Valerie Aarne Grossman, Ronak Amir Sardari, Himal Subramanya, Sindhuja Kadambi, Elizabeth Belcher, Jared Kettinger, Mark A. O'Rourke, Elie G. Dib, Nicholas J. Vogelzang, William Dale, Supriya Mohile

Disclosures

The authors indicated no financial relationships.

References

1. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722–727.

2. Rockwood K, Howlett SE. Age-related deficit accumulation and the diseases of ageing. Mech Ageing Dev 2019;180:107–116.

3. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc 2010;58:681–687.

4. Handforth C, Clegg A, Young C et al. The prevalence and outcomes of frailty in older cancer patients: A systematic review. Ann Oncol 2015;26:1091–1101.

5. Kojima G, Iliffe S, Jivraj S et al. Association between frailty and quality of life among community-dwelling older people: A systematic review and meta-analysis. J Epidemiol Community Health 2016;70:716–721.

6. Rockwood K, Stadnyk K, MacKnight C et al. A brief clinical instrument to classify frailty in elderly people. Lancet 1999;353:205–206.

7. Ethun CG, Bilen MA, Jani AB et al. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67:362–377.

8. Mandelblatt JS, Cai L, Luta G et al. Frailty and long-term mortality of older breast cancer patients: CALGB 369901 (Alliance). Breast Cancer Res Treat 2017;164:107–117.

9. Williams GR, Deal AM, Sanoff HK et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer 2019;27:2693–2698.

10. Weiss Wiesel TR, Nelson CJ, Tew WP et al. The relationship between age, anxiety, and depression in older adults with cancer. Psychooncology 2015;24:712–717.

11. Unutzer J, Patrick DL, Simon G et al. Depressive symptoms and the cost of health services in HMO patients aged 65 years and older. A 4-year prospective study. JAMA 1997;277:1618–1623.

12. Druss BG, Rohrbaugh RM, Rosenheck RA. Depressive symptoms and health costs in older medical patients. Am J Psychiatry 1999;156:477–479.

13. Langa KM, Valenstein MA, Fendrick AM et al. Extent and cost of informal caregiving for older Americans with symptoms of depression. Am J Psychiatry 2004;161:857–863.

14. Gallo JJ, Anthony JC, Muthen BO. Age differences in the symptoms of depression: A latent trait analysis. J Gerontol 1994;49:P251–P264.

15. Kissane DW, Maj M, Sartorius N. Depression and cancer. Chichester, West Sussex, UK: Wiley, 2011:xiv, 244 p.

16. Weinberger MI, Roth AJ, Nelson CJ. Untangling the complexities of depression diagnosis in older cancer patients. ***The Oncologist*** 2009;14:60–66.

17. Saracino RM, Weinberger MI, Roth AJ et al. Assessing depression in a geriatric cancer population. Psychooncology 2017;26:1484–1490.

18. Klepin HD, Tooze JA, Pardee TS et al. Effect of intensive chemotherapy on physical, cognitive, and emotional health of older adults with acute myeloid leukemia. J Am Geriatr Soc 2016;64:1988–1995.

19. Nelson CJ, Balk EM, Roth AJ. Distress, anxiety, depression, and emotional well-being in African-American men with prostate cancer. Psychooncology 2010;19:1052–1060.

20. Teunissen SC, de Haes HC, Voest EE et al. Does age matter in palliative care? Crit Rev Oncol Hemat 2006;60:152–158.

21. Trevino KM, Saracino RM, Roth AJ. Symptomatology, assessment, and treatment of anxiety in older adults with cancer. J Geriatr Oncol 2021;12:316–319.

22. Chan CMH, Ahmad WAW, Yusof MMD et al. Effects of depression and anxiety on mortality in a mixed cancer group: A longitudinal approach using standardised diagnostic interviews. Psychooncology 2015;24:718–725.

23. Delgado-Guay M, Parsons HA, Li Z et al. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 2009;17:573–579.

24. Smith EM, Gomm SA, Dickens CM. Assessing the independent contribution to quality of life from anxiety and depression in patients with advanced cancer. Palliat Med 2003;17:509–513.

25. Hurria A, Li D, Hansen K et al. Distress in older patients with cancer. J Clin Oncol 2009;27:4346–4351.

26. Sousa ACPD, Dias RC, Maciel ACC et al. Frailty syndrome and associated factors in

© 2021 AlphaMed Press.

15494490, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

community-dwelling elderly in northeast Brazil. Arch Gerontol Geriat 2012;54:E95–E101.

27. Gurina NA, Frolova EV, Degryse JM. A roadmap of aging in Russia: The prevalence of frailty in community-dwelling older adults in the St. Petersburg district-the "crystal" study. J Am Geriatr Soc 2011;59:980–988.

28. Pegorari MS, Tavares DMD. Factors associated with the frailty syndrome in elderly individuals living in the urban area. Rev Lat Am Enfermagem 2014;22:874–882.

29. Mohile SG, Epstein RM, Hurria A et al. Communication with older patients with cancer using geriatric assessment: A cluster-randomized clinical trial from the national cancer institute community oncology research program. JAMA Oncol 2020;6:196–204.

30. Loh KP, Mohile SG, Lund JL et al. Beliefs about advanced cancer curability in older patients, their caregivers, and oncologists. ***The Oncologist*** 2019;24:E292–E302.

31. Hernandez Torres C, Hsu T. Comprehensive geriatric assessment in the older adult with cancer: A review. Eur Urol Focus 2017;3:330–339.

32. Loh KP, Soto-Perez-de-Celis E, Hsu T et al. What every oncologist should know about geriatric assessment for older patients with cancer: Young International Society of Geriatric Oncology position paper. J Oncol Pract 2018;14:85–94.

33. Greenberg SA. The geriatric depression scale (GDS). Hartford Institute for Geriatric Nursing, NYU College of Nursing 2012:2. Available at https://hign.org/consultgeri/try-this-series/geriatric-depression-scale-gds. Accessed April 12,2020.

34. Wild B, Eckl A, Herzog W et al. Assessing generalized anxiety disorder in elderly people using the GAD-7 and GAD-2 scales: Results of a validation study. Am J Geriat Psychiat 2014;22:1029–1038.

35. Hurria A, Li DN, Hansen K et al. Distress in older patients with cancer. J Clin Oncol 2009;27:4346–4351.

36. Searle SD, Mitnitski A, Gahbauer EA et al. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.

37. Cohen HJ, Smith D, Sun CL et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer 2016;122:3865–3872.

38. Akaike H. Citation classic - a new look at the statistical-model identification. Cc/Eng Tech Appl Sci 1981;51:22.

39. Atkinson AC. Likelihood ratios, posterior odds and information criteria. J Econometrics 1981;16:15–20.

40. Shtatland ES, Kleinman K & Cain EM Stepwise methods in using SAS Proc Logistic and SAS Enterpise Miner for prediction. SUGI 28;Paper 258-28

41. Jeste DV. Frailty and mental health: Association with cognition, sleep, and well-being in older adults. Int Psychogeriatr 2019;31:755–757.

42. Buigues C, Padilla-Sanchez C, Garrido JF et al. The relationship between depression and frailty syndrome: A systematic review. Aging Ment Health 2015;19:762–772.

43. Wang XH, Shen KJ. The reciprocal relationship between frailty and depressive symptoms among older adults in rural China: A cross-lag analysis. Healthcare (Basel) 2021;9:593.

44. De Vriendt P, Peersman W, Florus A et al. Improving health related quality of life and independence in community dwelling frail older adults through a client-centred and activity-oriented program. A pragmatic randomized controlled trial. J Nutr Health Aging 2016;20:35–40.

45. Apostolo J, Cooke R, Bobrowicz-Campos E et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: A systematic review. JBI Database System Rev Implement Rep 2018;16:140–232.

46. Cohen HJ, Feussner JR, Weinberger M et al. A controlled trial of inpatient and outpatient geriatric evaluation and management. New Engl J Med 2002;346:905–912.

47. Monteserin R, Brotons C, Moral I et al. Effectiveness of a geriatric intervention in primary care: A randomized clinical trial. Fam Pract 2010;27:239–245.

48. Magnuson A, Allore H, Cohen HJ et al. Geriatric assessment with management in cancer care: Current evidence and potential mechanisms for future research. J Geriatr Oncol 2016;7:242–248.

49. Rodin G, An E, Shnall J et al. Psychological interventions for patients with advanced disease: Implications for oncology and palliative care. J Clin Oncol 2020;38:885–904.

50. Faller H, Schuler M, Richard M et al. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: Systematic review and meta-analysis. J Clin Oncol 2013;31:782–793.

51. Mohile SG, Dale W, Somerfield MR et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018;36:2326–2347.

52. Walston J, Buta B, Xue QL. Frailty screening and interventions: Considerations for clinical practice. Clin Geriatr Med 2018;34:25–38.

© 2021 AlphaMed Press.

1549490x, 2021, 12, Downloaded from https://theoncologist.onlinelibrary.wiley.com/doi/10.1002/onco.13975 by CochraneChina, Wiley Online Library on [03/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License