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Fatigue is Independently Associated with Functional Status Limitations in Older Adults with Gastrointestinal Malignancies – results from the CARE Registry

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Abstract

Purpose: Fatigue is a component of frailty and may undermine functional well-being and independent living. The prevalence of fatigue and its impact on functional limitations among older adults with cancer remains understudied.

Methods: Using participants enrolled in the Cancer and Aging Resilience Evaluation (CARE), a prospective registry of patients (< 60y) with cancer, who underwent a geriatric assessment (GA) at the first visit with oncology, we examined the presence of fatigue based on self-report of moderate to severe fatigue on PROMIS global health 10-item instrument at the time of GA. We examined the association of fatigue with impairments in Instrumental Activities of Daily Living (IADL) and

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Authors’ contributions:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Grant R. Williams], [Mustafa AL-Obaidi] [Chen Dai] and [Smith Giri].

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Activities of Daily Living (ADL) adjusting for age, sex, race/ethnicity, education, cancer type and stage, pain, comorbidities, and time from cancer.

Results: We included 374 older adults with cancer with a median age of 70y; 56% were male and 23% black. Diagnoses included colorectal (33%) and pancreatic cancers (25%), with most patients with advanced stage disease (71% stage III/IV). Overall, 210 (58%) patients reported significant fatigue. Patients reporting significant fatigue had an increased odds of IADL (adjusted Odds Ratio, aOR 1.9; 95% CI 1.1–3.2) or ADL impairment (aOR 3.6; 95% CI 1.4–9.3), as compared to those without, after adjusting for aforementioned confounders.

Conclusions: Over half of older adults with cancer reported moderate to severe fatigue that was independently associated with functional status limitations. Further understanding of the multifaceted aspects of fatigue and development of interventions combating fatigue in this population is urgently needed.

Keywords

fatigue; functional status; geriatric oncology; aging; cancer; geriatric assessment

Introduction

Older adults represent the vast majority of newly diagnosed cancer as well as cancer deaths in the US [1]. In addition, the fastest growing cancer population is among adults aged 85 years and older [2]. Older adults comprise a heterogeneous population with respect to health status as well as social support that is not routinely captured in traditional oncologic evaluations [3 4]. Older adults vary in their preferences regarding oncologic treatment plans. Although prolonging life is important to older patients with cancer, 44% value other outcomes as more important than survival [5]. Over half of older adults with cancer would rather live a shorter life than lose their ability to take care of themselves and nearly three quarters with serious illness would not choose a life-prolonging therapy if it resulted in severe functional impairment [5 6].

Cancer-related fatigue is commonly defined as a subjective sense of tiredness or exhaustion related to cancer or its treatment that is disproportionate to recent activity [7]. Fatigue is common and often described as the most distressing symptom associated with cancer and cancer treatments, which can persist for years after treatment [8 9]. Fatigue is one of the five components of the frailty phenotype originally proposed by Fried *et al* [10 11]. Moreover, fatigue is associated with many adverse outcomes including functional limitations, disability, and mortality in the general older adult population and has been proposed as an early indicator of aging [12]. However, the underlying physiologic mechanisms of cancer-related fatigue and how this is similar or different from age-related fatigue has not yet been elucidated. As such, no mechanistically driven fatigue interventions exist [13]. Furthermore, the burden of fatigue and its impact on functional well-being among the growing number of older adults with cancer remains poorly understood.

In this study, we aimed to 1) describe the burden of fatigue among older adults with cancer, 2) evaluate its association with other geriatric assessment (GA) identified impairments,

frailty, health-related quality of life (HRQoL), and self-reported healthcare utilization, and 3) examine its relationship with functional status impairments.

Methods

Study Population

This is a cross-sectional analysis of participants enrolled in a prospective study of older adults with cancer at the University of Alabama at Birmingham (Cancer & Ageing Resilience Evaluation, UAB CARE Registry). The development and integration of CARE registry into routine clinical practice at UAB is described elsewhere [14]. Adults 60 years and older completed a patient-reported GA assessment at the time of initial consultation with a medical oncologist. For the purpose of this analysis, we included patients enrolled in the CARE registry between September 2017 and January 2020 with a GI malignancy who underwent GA prior to any planned systemic therapy. The institutional review board at UAB approved this study and all participants provided written consent prior to participation (IRB-300000092).

Geriatric Assessment

The CARE GA tool represents a modified, patient-reported version of the Cancer and Aging Research Group (CARG) GA tool originally pioneered by Dr. Hurria.[15] The CARE GA tool includes a systematic assessment of falls, functional status, nutrition, social support, psychological health, patient-reported cognitive complaints, social activities, patient-reported eastern cooperative oncology group (ECOG) performance status, polypharmacy and comorbid conditions (using the Older Americans Resources and Services [OARS] comorbidity tool and dichotomized as <3 or ≥ 3) [3 14 16]. Previously published domain-specific cut-offs were utilized [3 14 17]. The individual domains along with the cut-offs are detailed in the Supplement. We used 44 items included in the GA to develop a frailty index based on the principles of deficit accumulation; standard threshold scoring was applied (frail >0.35) [18–20]. Frailty indices using this method have been associated with increased mortality, increased severe chemotherapy toxicities, and reduced HRQoL [19–21].

Fatigue

As part of the GA, patients were asked to complete the National Institutes of Health's 10-item Patient-Reported Outcomes Measurement Information System (PROMIS®) global health scale (PROMIS Global 10) short-form to assess HRQoL.[22] PROMIS Global 10 incorporates a question on fatigue: "*In the past 7 days, how would you rate your fatigue on average?*" Response range from none, mild, moderate, severe, to very severe. Consistent with prior reports [23 24], we classified presence of significant fatigue as self-report of at least moderate or higher degree of fatigue whereas a response of none or mild fatigue was categorized as no significant fatigue.

Functional Status

We measured functional status using the Older Americans Resources and Services (OARS) assessment [25]. Specifically, we used a 6-item measure of instrumental activities of daily living (IADL) that included an assessment of driving/traveling, shopping, preparing meals,

house-work, taking medicines, and handling money, and a 3-item measure of activities of daily living (ADL) that included getting in/out of bed, ability to dress/undress, and to take a bath or shower. The response to each item included the ability to perform the task without help, with some help, or unable to perform the independently. We defined any limitation (either some help or completely unable) within any of the IADL and ADL measures as being an impairment within that domain.

Other covariates

We used PROMIS® global-10 to measure HRQoL, which includes separate scoring for physical and mental health subscales and has been tested previously in large samples of adults in the US [22 26]. The item responses were converted to T-scores with a standardized mean score of 50 and a standard deviation (SD) of 10. The minimal clinically relevant difference for PROMIS ranges from 2 to 6 points, and a score of 40 or less (1 standard deviation) is considered impaired for the physical and mental subscales [27]. We measured healthcare utilization by asking participants whether they had been seen in the emergency room (ER) or hospitalized in the past year. Race, ethnicity, education level, employment, and marital status self-reported. We abstracted cancer stage, cancer type, date of diagnosis, and treatment status from the electronic medical record.

Statistical Analyses

We used descriptive statistics to summarize the demographic and clinical characteristics of the study participants. We measured the proportion of patients with significant fatigue and computed the 95% confidence interval (95%CI) using exact binomial (Clopper-Pearson) method [28]. We examined group differences in demographic, clinical, geriatric assessment domain impairments, frailty, HRQoL, and healthcare utilization using Analysis of Variance/Wilcoxon Rank Sum test for continuous variables and Chi-squared test/Fisher's exact test for categorical variables. We used logistic regression models to examine the association between fatigue and limitations in IADL and ADL in separate models adjusting a priori for potential confounders within the literature including age, sex, race/ethnicity, education, cancer type and stage, pain, multi-morbidity, and time from cancer diagnosis. All statistical tests were two-sided and the level of significance was set at 0.05. All analyses used SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Overall, 650 adults were diagnosed with a GI malignancy at age 60y were seen at the UAB GI Oncology clinic for initial consultation during the study period; of these 556 (85%) were enrolled in the CARE registry. Of these, 364 participants underwent GA evaluation prior to starting anti-cancer therapy and were included in the current study (Figure 1). Mean age at study enrollment was 70.1y (SD, 7.26y); 56% of the cohort was male and 23% were Black (Table 1). The most common tumor types included colorectal (22.1%) and pancreatic (17.8%) and majority of participants had stage III/IV disease (70%).

Association of fatigue with demographic and clinical characteristics

Overall, 12.1% of participants reported no fatigue, 30.2% reported mild, 35.7% moderate, 16.8% severe, and 5.2% very severe fatigue (Figure 2). Based on this, 57.8% (95%CI 52.4–62.8%) of the patients reported moderate to severe fatigue. We found no associations between moderate to severe fatigue and sex, race/ethnicity, marital status, or cancer type. However, patients with moderate to severe fatigue were more likely to be diagnosed with advanced stage cancer (stage IV 51% vs. 39% $p=.005$) and to be on disability (20% vs. 5%, $p<.001$) (Table 1).

Bivariate association of fatigue with ADL/IADL and additional GA impairments

The prevalence of ADL and IADL impairment in the overall cohort was 17.7% (95%CI 13.9–22.1%) and 50.7% (95%CI 45.4–56.1%), respectively. Patients reporting moderate to severe fatigue were more likely to report functional impairments in terms of both IADL (64.7% vs. 32.0%; $p<.001$) and ADL limitations (27.5% vs. 4.6%; $p<.001$). Patients with moderate to severe fatigue were also more likely to report multiple GA impairments. These impairments included 1 fall in the last 6 months (28.4% vs. 9.5%, $p<.001$), limitations in walking one block (71.2% vs. 29.8%; $p<.001$), 3 comorbid conditions (62.4% vs. 38.8%; $p<.001$), malnutrition (66.7% vs. 31.9%; $p<.001$), cognitive complaints (10.9% vs. 0.7%; $p<.001$), limitations in social activities (36.1% vs. 7.9%; $p<.001$), anxiety (26.7% vs. 7.4%; $p<.001$), depression (20.8% vs. 2.0%; $p<.001$), moderate/severe pain (63.3% vs. 20.4%; $p<.001$), and frailty (53.8% vs. 9.7%; $p<.001$). Finally, patients reporting moderate to severe fatigue were more likely to report hospitalizations (72.2% vs. 54.3%, $p<.001$) and ER visits (65.0% vs. 46.4%, $p<.001$) in the 12 months prior to study participation (Table 2).

Multivariable analyses adjusted for age, sex, education, cancer type and stage, pain, comorbid conditions, and time from cancer diagnosis, revealed higher odds of IADL and ADL impairment in those with moderate to severe fatigue (OR=1.9, 95%CI 1.1–3.2, $p=0.03$; OR=3.6, 95%CI 1.4–9.3, $p=0.007$, respectively), compared with those with no/mild fatigue (Table 3).

Discussion

In this study, we show that over half of the older adults with GI malignancies report moderate to severe fatigue. Further, fatigue is associated with multiple GA identified impairments including functional limitations, reduced physical and mental HRQoL, and higher rates of prior healthcare utilization.

The prevalence of fatigue in our study is consistent with previous literature on cancer-related fatigue. Prior estimates report 60–96% of patients with cancer undergoing treatment experience fatigue.[8 9] In the few other studies that have explored fatigue in the older adult cancer population, a similar prevalence was found [29 30]. In a study by Respini *et al* of 80 older adults undergoing chemotherapy, 72.7% reported fatigue; there was an association between fatigue and depressive symptoms. Interestingly, they found that female patients had higher fatigue levels than males in their population, whereas we found no sex differences in our population [29]. In a prior study of older adults with cancer by Luciani *et al*, fatigue

was associated with ADL and IADL impairment; the authors suggested that fatigue was a mediator of functional dependence. However, they did not account for comorbid conditions, pain, or cancer types as our analyses included and they had a smaller sample population [30]. In addition, in a recent by Pisu *et al* of the most impactful factors of HRQoL in older adults with cancer, fatigue was the strongest predictor of both physical and mental HRQoL [31]. Similarly, results in the broader gerontology literature have shown similar association of fatigue with functional status limitations [32 33]. Moreover, prior studies have clearly shown that fatigue rarely occurs in isolation and often occurs as part of a symptom cluster that includes pain, emotional distress, and sleep disturbances [7]. Thus, our findings demonstrating uniform and strong associations with all GA impairments measured is not surprising, and should raise attention to the potential negative impact of cancer-related fatigue in the older adult population [7]. As functional independence is a priority for older adults and strongly associated with increased chemotherapy toxicities and reduced survival, further understanding the determinants of functional limitations and developing targeted interventions is critical [34].

Guidelines for management of cancer-related fatigue suggest early recognition and management [7]. Patients found to have fatigue should undergo a comprehensive history and evaluation with a focus on the treatable contributing factors, such as pain, anemia, emotional distress, malnutrition, medication side effect, and deconditioning. Many potential therapeutic treatments exist for cancer-related fatigue and clinical trials have explored a variety of interventions. Overall, physical activity and exercise-based interventions have shown the most promise both during and post cancer treatment [7 35]. However, the optimal type, intensity, and timing of exercise/physical activity interventions remains unknown [35]. Psychosocial interventions, such as cognitive behavioral therapy and mindfulness-based stress reduction, have also demonstrated improvements in fatigue [36]. In addition, pharmacologic approaches involving psychostimulants (such as methylphenidate) can be considered after ruling out other causes of fatigue and treating the above reversible causes [37]. However, the use of psychostimulants is potentially problematic in the older adult population, and if utilized, a management philosophy of “start low and go slow” is recommended to reduce the risk of unintended side effects. Few to no intervention studies have focused specifically on the older adult cancer population, and given older adults with cancer are potentially at higher risk of fatigue and related adverse events, such as functional decline, a more focused approach to interventions in this population is warranted.

Our study has limitations. The cross-sectional nature of our study limits any determination of causality or directionality of our findings. Our sample derives from a single site in the Southeastern US and consists of only GI malignancies, and our findings may not be representative of other populations. Although a high proportion of the eligible population enrolled in CARE (over 90%)[38], there remains some concern for potential selection bias. In addition, the fatigue reported in this older adult cancer population is both a combination of aging-related fatigue as well as cancer-related fatigue. Without a non-cancer control population and/or longitudinal analyses, differentiating these two important and distinct causes of fatigue is not possible. Lastly, the CARE survey is patient-reported GA and although a standard approach in geriatric oncology, the survey is not validated against objective testing.

In conclusion, fatigue is highly prevalent in older adults with GI malignancies and is associated with numerous adverse outcomes. Fatigue may undermine functional independence in older adults with cancer, which is a high priority outcome for this vulnerable population. Further exploration of fatigue as a potential mediator of functional decline in longitudinal assessments in patients undergoing chemotherapy is needed and development of interventions tailored to the older adult is necessary to mitigate and manage fatigue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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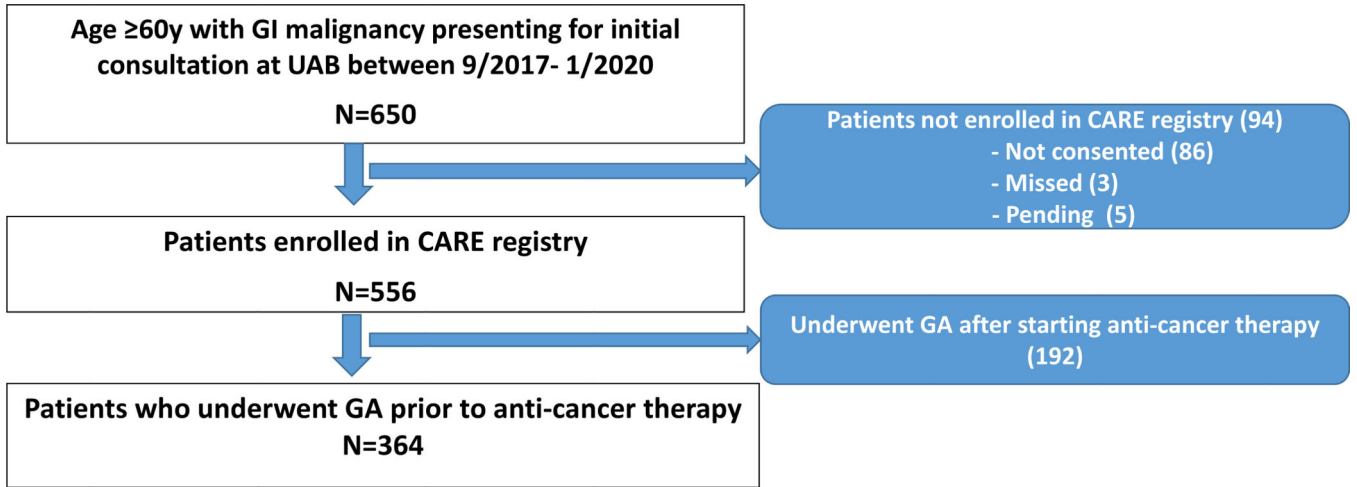


Figure 1: Flow Chart showing the process of study cohort selection. Overall, 650 patients were seen for initial consultation at the UAB GI Oncology clinic between 9/2017 and 1/2020, of which 364 were enrolled in CARE registry and underwent geriatric assessment prior to starting systemic anti-cancer therapy.

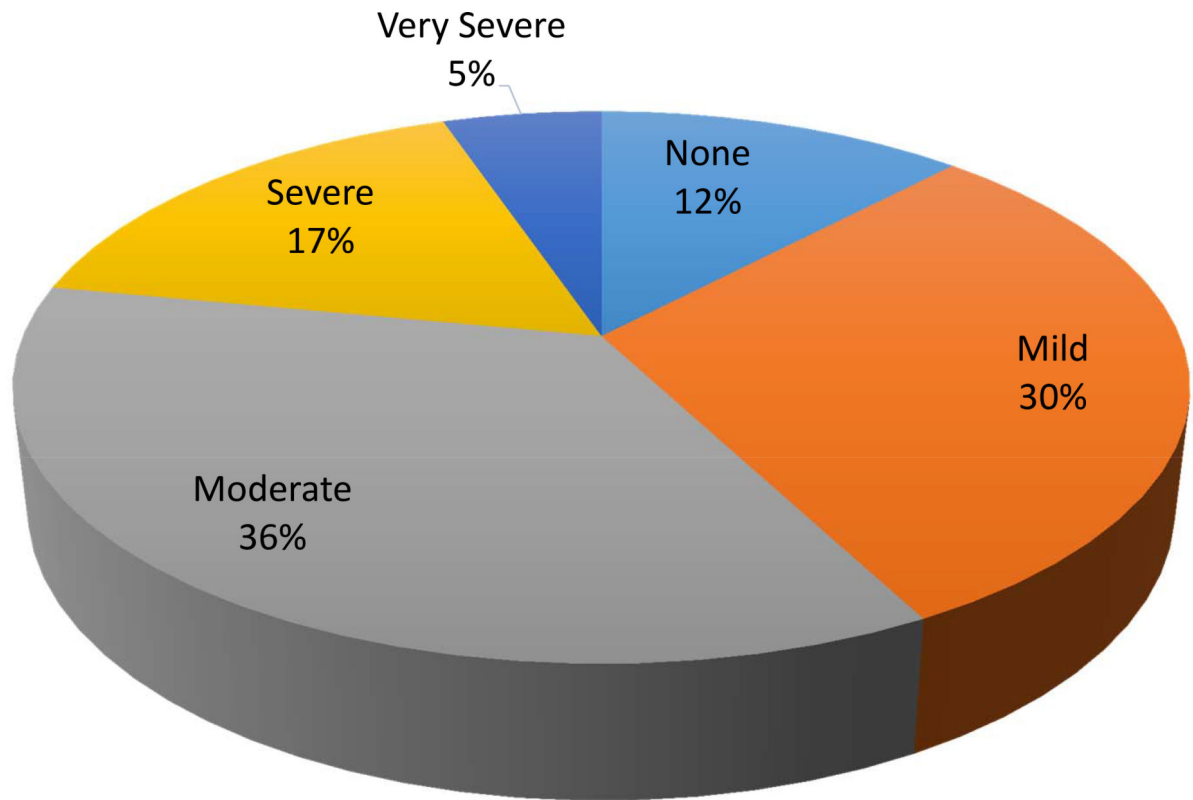


Figure 2: Original responses of study participants to the single item fatigue question, “In the past 7 days, how would you rate your fatigue on average?” Overall, 58% reported having at least moderate or higher-grade fatigue.

Table 1.

Patient Demographics and Characteristics

	All patients (n= 364)	None/mild fatigue (n=154)	Moderate-very Severe fatigue (n=210)	<i>p</i> *
Age, mean (SD)	70.1 (7.3)	69.7 (7.1)	70.5 (7.3)	0.34
Age, n (%)				0.90
60–64	97 (26.6)	43 (27.9)	54 (25.7)	
65–69	84 (23.1)	36 (23.4)	48 (22.9)	
70–74	83 (22.8)	36 (23.4)	47 (22.4)	
75–79	55 (15.1)	23 (14.9)	32 (15.2)	
80+	45 (12.4)	16 (10.4)	29 (13.8)	
Sex, n (%)				0.31
Male	205 (56.3)	82 (53.2)	123 (58.6)	
Race, n (%)				0.46
White	274 (75.3)	119 (77.3)	155 (73.8)	
Black	85 (23.4)	32 (20.8)	53 (25.2)	
Other	5 (1.4)	3 (1.9)	2 (1.0)	
Ethnicity, n (%)				0.78
Hispanic	8 (2.2)	3 (1.9)	5 (2.4)	
Educational level, n (%)				0.11
Less than high school	65 (17.9)	21 (13.6)	44 (21.0)	
High school graduate	96 (26.4)	43 (27.9)	53 (25.2)	
Some college	67 (18.4)	24 (15.6)	43 (20.5)	
Associate/bachelors	101 (27.7)	46 (29.9)	55 (26.2)	
Advanced degree	35 (9.6)	20 (13.0)	15 (7.1)	
Marital status, n (%)				0.20
Single	26 (7.1)	10 (6.5)	16 (7.6)	
Widowed/divorced	104 (28.6)	37 (24.0)	67 (31.9)	
Married	234 (64.3)	107 (69.5)	127 (60.5)	
Employment, n (%)				<.001
Retired	222 (61.0)	99 (64.3)	123 (58.6)	
Disabled	50 (13.7)	8 (5.2)	42 (20.0)	
Part-time (<32hr/wk)	10 (2.7)	5 (3.2)	5 (2.4)	
Full-time (>32hr/wk)	38 (10.4)	25 (16.2)	13 (6.2)	
Other	44 (12.1)	17 (11.0)	27 (12.9)	
Cancer type, n (%)				0.79
Colorectal	121 (33.2)	56 (36.4)	65 (31.0)	
Pancreatic	90 (24.7)	36 (23.4)	54 (25.7)	
Hepatobiliary	61 (16.8)	25 (16.2)	36 (17.1)	
Gastroesophageal	39 (10.7)	14 (9.1)	25 (11.9)	
Other	53 (14.6)	23 (14.9)	30 (14.3)	
Cancer stage, n (%)				.006
I/II	107 (29.4)	44 (28.6)	63 (30.0)	
III	93 (25.5)	52 (33.8)	41 (19.5)	
IV	164 (45.1)	58 (37.7)	106 (50.5)	

* *p*-value from the bivariate comparison of those with and without fatigue

Abbreviations: SD, Standard deviation

Table 2.

Geriatric Assessment, Health-Related Quality of Life, and Healthcare Utilization differences in those with and without moderate/severe fatigue.

	Overall (n= 364)	None / Mild fatigue (n=154)	Moderate / Severe fatigue (n=210)	<i>p</i>
Geriatric Assessment Domain				
Any IADL dependence, n(%)	178 (50.7)	48 (32.0)	130 (64.7)	<.001
Any ADL dependence, n(%)	63 (17.7)	7 (4.6)	56 (27.5)	<.001
Falls (≥ 1), n(%)	70 (20.3)	14 (9.5)	56 (28.4)	<.001
Reported limitations in walking one block, n(%)	191 (53.7)	45 (29.8)	146 (71.2)	<.001
Impaired ecog ps (≤ 2), n(%)	120 (33.7)	13 (8.6)	107 (52.2)	<.001
Medications (≥ 9 daily), n(%)	87 (24.6)	23 (15.1)	64 (31.7)	<.001
Comorbidities (≥ 3), n(%)	185 (52.3)	59 (38.8)	126 (62.4)	<.001
Malnutrition, n(%)	173 (52.0)	45 (31.9)	128 (66.7)	<.001
Cognitive complaints (mod/sev.), n(%)	23 (6.5)	1 (0.7)	22 (10.9)	<.001
Limitations in social activities, n(%)	85 (24.0)	12 (7.9)	73 (36.1)	<.001
Anxiety (mod/sev.), n(%)	65 (18.5)	11 (7.4)	54 (26.7)	<.001
Depression (mod/sev.), n(%)	45 (12.8)	3 (2.0)	42 (20.8)	<.001
Pain (mod/sev), n(%)	162 (45.1)	31 (20.4)	131 (63.3)	<.001
Frailty Index (frail), n(%)	128 (35.2)	15 (9.7)	113 (53.8)	<.001
Health-Related Quality of Life				
Overall self-reported health (fair/poor), n (%)	159 (44.0)	25 (16.2)	134 (64.7)	<.001
Physical Health sub-score, mean (SD)	42.9 (10.8)	51.8 (7.7)	36.2 (7.4)	<.001
Mental Health sub-score, mean (SD)	47.9 (9.6)	54.0 (8.0)	43.3 (8.0)	<.001
Healthcare Utilization				
Hospitalized in the last year, n(%)	230 (64.6)	82 (54.3)	148 (72.2)	<.001
ER visit in the last year, n(%)	200 (57.0)	70 (46.4)	130 (65.0)	<.001

* *p*-value from the bivariate comparison of those with moderate/severe versus none/mild fatigue

Abbreviations: IADL, instrumental activities of daily living; ADL; activities of daily living; ecog ps, eastern cooperative oncology group performance status; mod/sev, moderate/severe; ER, emergency room.

Table 3.

Multivariable model of associations of moderate/severe fatigue with impairments in instrumental activities of daily living and activities of daily living

Variable	Adjusted OR	95 % CI of OR	<i>p</i>
Instrumental Activities of Daily Living Model			
IADL impairment	1.9	1.1–3.2	0.032
Age group			
60–64	Ref	Ref	0.85
65–69	0.9	0.4–1.9	0.93
70–74	0.9	0.5–1.9	0.34
75–79	1.0	0.4–2.5	0.34
80+	1.6	0.6–3.9	
Sex			
Female	0.8	0.5–1.3	0.34
Education			
Less than HS	Ref	Ref	0.59
HS graduate	0.8	0.3–1.8	0.35
Some college	1.6	0.6–4.0	0.65
Associate/Bachelors	1.2	0.5–2.8	0.66
Advanced Degree	0.8	0.3–2.3	
Pain			
0–3	Ref	Ref	<0.001
>3	5.6	3.1–10.2	
Comorbidity			
0–2	Ref	Ref	0.002
3	2.3	1.4–4.0	
Cancer type			
Colorectal	Ref	Ref	0.52
Pancreatic	0.8	0.4–1.6	0.92
Hepatobiliary	1.0	0.4–2.1	0.10
Gastroesophageal	2.2	0.9–5.5	0.59
Other	0.8	0.4–1.8	
Cancer stage			
0-II	Ref	Ref	0.9
III	0.5	1.1	0.46
IV	1.3	2.4	
Days from diagnosis to GA	1.0	1.0	0.35
Activities of Daily Living Model			
ADL impairment	3.6	1.4–9.3	0.007
Age group			
60–64	Ref	Ref	0.90
65–69	1.0	0.5–2.0	0.96
70–74	1.0	0.5–2.0	0.85
75–79	1.1	0.5–2.6	0.25
80+	1.7	0.7–4.2	
Sex			
Female	0.83	0.5–1.4	0.25
Education			
Less than HS	Ref	Ref	0.46
HS graduate	0.7	0.3–1.7	0.45
Some college	1.4	0.6–3.7	0.65
Associate/Bachelors	1.2	0.5–2.8	0.73
Advanced Degree	0.8	0.3–2.4	
Pain			
0–3	Ref	Ref	<0.001
>3	5.9	3.3–10.5	

Variable	Adjusted OR	95 % CI of OR	<i>p</i>
Comorbidity 0-2 3	Ref 2.4	Ref 1.4-4.1	0.001
Cancer type	Ref	Ref	0.54
Colorectal	0.8	0.4-1.6	0.82
Pancreatic	0.9	0.4-2.0	0.15
Hepatobiliary	2.0	0.8-5.2	0.55
Gastroesophageal	0.8	0.3-1.8	
Other			
Cancer stage	Ref	Ref	0.09
0-II	0.5	0.3-1.1	0.32
III	1.4	0.7-2.6	
IV			
Days from diagnosis to GA	1.0	1.0-1.0	0.49

Abbreviations: IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; OR, Odds Ratio

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