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FRAILTY AS DETERMINED BY A COMPREHENSIVE GERIATRIC ASSESSMENT DERIVED DEFICIT ACCUMULATION INDEX IN OLDER PATIENTS WITH CANCER TREATED WITH CHEMOTHERAPY

Harvey Jay Cohen, MD,
Duke University Medical Center, Durham, NC 27710

David Smith, PhD,
QIMR Berghofer Medical Research Institute

Can-Lan Sun, PhD,
City of Hope Comprehensive Cancer Center and Beckman Research Institute

Julie Filo, BA,
City of Hope Comprehensive Cancer Center and Beckman Research Institute

Vani Katheria, MS,
City of Hope Comprehensive Cancer Center and Beckman Research Institute

Arti Hurria, MD,
City of Hope Comprehensive Cancer Center and Beckman Research Institute

William Tew, MD,
Memorial Sloan-Kettering Cancer Center

Stuart M. Lichtman, MD,
Memorial Sloan-Kettering Cancer Center

Supriya G. Mohile,
University of Rochester Medical Center, Rochester

Corresponding Author: Harvey Jay Cohen, MD, Duke University Medical Center, Center for the Study of Aging and Human Development, 201 Trent Drive, Box 3003, Durham, NC 27710, Office: 919-660-7502, Fax: 919-684-8569, harvey.cohen@duke.edu.

The authors have contributed to the manuscript as follows:
Conceptualization
HJC; AH;
Methodology
HJC; AH; VK; JF; AG; SML; CPG; HDK; CO; SGM; WT; DS; CS
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DS; CS
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HJC; AH; VK; JF; AG; SML; CPG; HDK; CO; SGM; WT; DS; CS
Writing Original Draft
HJC; AH
Writing – Review and Editing
HJC; AH; VK; JF; AG; SML; CPG; HDK; CO; SGM; WT; DS; CS
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HJC; AH; VK; JF; AG; SML; CPG; HDK; CO; SGM; WT; DS: CS

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Cynthia Owusu, MD,
Case Western Reserve University, Cleveland OH

Heidi D. Klepin, MD,
Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem NC

Cary P. Gross, MD, and
Yale School of Medicine, New Haven CT

Ajeet Gajra, MD
State University of New York Upstate Medical University and Veterans Administration Medical Center, Syracuse NY

For the Cancer and Aging Research Group

Harvey Jay Cohen: harvey.cohen@duke.edu; David Smith: david.smith@qimrberghofer.edu.au; Can-Lan Sun: casun@coh.org; Julie Filo: julie.filo@yahoo.com; Vani Katheria: vkatheria@coh.org; Arti Hurria: AHurria@coh.org; William Tew: teww@mskcc.org; Stuart M. Lichtman: LichtmaS@mskcc.org; Supriya G. Mohile: supriya_mohile@urmc.rochester.edu; Cynthia Owusu: Cynthia.Owusu@UHhospitals.org; Heidi D. Klepin: hklepin@wakehealth.edu; Cary P. Gross: cary.gross@yale.edu; Ajeet Gajra: gajraa@upstate.edu

Abstract

Background—Frailty has been suggested as a construct for oncologists to consider in treating older cancer patients. Therefore we assessed the potential of creating a Deficit Accumulation Frailty Index (DAFI) from a largely self-administered comprehensive geriatric assessment (CGA).

PATIENTS AND METHODS—Five hundred patients age 65 and older received a CGA prior to receiving chemotherapy. A DAFI was constructed resulting in a 51 item scale and cut points for robust/non frail (0.0< 0.2), pre-frail (0.2<0.35) and frail (≥0.35) were examined.

RESULTS—Two Hundred and Fifty patients (50%) were non-frail, 197 (39%) pre-frail, 52 (11%) frail. Older patients (80+), lower education, living alone, and higher stage were associated with pre-frail/frail. Pre-frail/frail patient were more likely to have grade 3+ toxicity, but not to have dose delay or reduction, and were more likely to discontinue drug and be hospitalized. The association with grade 3+ toxicity was attenuated by controlling for a toxicity risk calculator but the other outcomes were not.

CONCLUSION—A Deficit Accumulation Frailty Index can be constructed from a CGA in older cancer patients and can indicate the frailty status of the population. The frailty status so determined is associated both with outcomes likely due to chemotherapy toxicity as well as those likely due to age related physiologic and functional deficits and thus can be useful in the overall assessment of the patient.

Keywords

Frailty; Cancer; Geriatric; Comprehensive Geriatric Assessment; Deficit Accumulation Index

Introduction

A recent IOM Report emphasized that the increasing incidence of cancer in the United States, largely a product of the increased incidence of cancer with aging and the rapidly aging demographic of the country, is one of our major challenges in achieving quality cancer

care.(1,2) The thirteen percent of people over the age of 65 comprise over fifty-three percent of new cancer incidence and almost seventy percent of cancer deaths.(1) Moreover, such older people constitute a very heterogeneous population with people of similar age varying widely in health status, functional status, expected survival, and quality of life.(3) Frailty has been suggested as a framework for understanding when a health state of vulnerability exists for an older individual.(4) This may be of value as oncologists contemplate treatment for older cancer patients, as a way to determine where on the spectrum a patient lies, to facilitate planning management approaches.

Geriatricians have long used a Comprehensive Geriatric Assessment (CGA) as a way to gather data to best characterize older individuals,(6) and in recent years this approach has been applied to older cancer patients.(7,8) We have previously reported the use of a largely self-administered CGA instrument, shown its feasibility and utility in the setting of cancer clinical trials, and demonstrated that information from this assessment can allow for prediction of chemotherapy toxicity.(9,10,11) Rockwood and colleagues have shown that a Frailty Index based on a deficits accumulation principle (i.e. using information from a substantial number of indicators of a person's health) can be calculated from information in a CGA in non-cancer patients, and used to predict subsequent events such as length of stay, functional status and mortality.(12,13)

Since such an index could provide a summary measure of vulnerability in cancer patients undergoing treatment, in this study, we sought to demonstrate the feasibility of calculating a Deficit Accumulation Frailty Index from information collected in a study administering CGA to 500 older cancer patients prior to the start of a new chemotherapy regimen, (11) We then determined whether frailty status determined by the index is associated with direct chemotherapy-related as well as more traditional geriatric outcomes, such as hospitalizations.

Methods

The study population and CGA measure have been previously described.(11) In brief, the study "Determining the Utility of an Assessment Tool for older Adults with Cancer" enrolled patient recruited from outpatient oncology practices, from seven participating institutions. Patients were eligible if they were ≥65 years of age, had a diagnosis of cancer regardless of type, were scheduled to receive a new chemotherapy regimen, and were English speaking. Out of 500 patients enrolled, 56% were female, 29% had lung, 27% gastrointestinal, 17% gynecological, 11% breast, and 10% genitourinary cancers, 61% had stage IV or extensive disease. Geriatric Assessment was performed prior to the initiation of chemotherapy and consisted of measures evaluating the domains of functional status, comorbidity, cognition, psychological state, social activity, social support, and nutrition.

The DAFI was constructed using the methods previously published for construction of an index from a CGA.(12–14) A 51-item scale was constructed by using individual items representing the various domains noted above. These items included assessment of activities of daily living, instrumental activities of daily living, level of physical activity, frequency of falls, number of medications, level of social activity and social support, disease status and

basic laboratory values. Variables were selected because they are associated with health status, generally increase with age, are not universal in older age, and cover a range of systems (14). The full list of items utilized is shown in Table 1, as well as the responses for what was considered a "positive" (i.e., marker of frailty) result. Most items involved binary answers and were coded as "0" if the adverse condition was absent and "1" if present. For those items with graded response (up to 3) e.g. not limited, limited a little, limited a lot, the absence of the condition was scored "0," the intermediate "1," and the most adverse "2.". (Figure 1 legend – calculation of the Frailty Index). The potential score ranges from 0 to 1.0. The frailty index per patient is calculated by summing across each item's non-missing scores divided by the sum of total possible scores across all non-missing items. If a patient completes all items, the denominator total is 78 points (Figure 1). The frailty index ranges from 0.0 to 1.0, where 0.0 corresponds to no frailty deficits detected. The items utilized for the construction of our scale were very similar to the items used from the CGA administered to general geriatrics patients reported by Song, et al with a greater than 86% overlap in items.(15) Cutpoints for the levels of frailty were utilized as per previous reports which have shown these or similar cut points to be associated with outcomes including mortality. (15–17) Our cutpoints were as follows: Robust/Non-frail: 0.0 < 0.2; Pre-frail: 0.2 < 0.35; Frail: ≥ 0.35. When we fit logistic regression to each outcome using the frailty index as the independent predictor, the Youden optimal cutpoint was comparable to the cutpoint between non-frail and prefrail, thus validating this as a reasonable cutpoint for comparisons.

Patients were followed from the beginning until the end of their course of chemotherapy with significant toxicity (grade 3 [severe], grade 4 [life-threatening], grade 5 [treatment-related death] by the National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] version 3.0), dose reductions, dose delays, treatment discontinuation, and hospitalizations captured at each clinical encounter.

Statistical Analysis

Chi-square tests were used to compare across categorized frailty index (robust/not frail, pre-frail, frail) for age (as categorical 65–69, 70–74, 75–79, 80–84, 85–91), sex (female, male), race (White vs, others), education (<=high school, college, graduate school), marital status (married, widowed, single/separated/divorced), living with companion (alone, with someone), employment (retired/homemaker/unemployed, the rest), cancer type (lung, GI, breast/GYN, GU/others), cancer stage (I/II, III, IV). Multinomial logistic regression was used to examine each variable univariately, and stepwise selection using entry and retention p value 0.10 was used to determine final factors associated with prefrailty and frailty in this population. All statistical tests were two-sided and p-values less than 0.05 were considered statistically significant.

For the five outcomes (grade 3+ toxicity (no/yes), dose reduction (no/yes), dose delays (no/yes), discontinuation of chemotherapy due to toxicity (no/yes), and hospitalization due to toxicity (no/yes), relative risks and 95% confidence intervals for categorized frailty index were calculated using a Poisson regression model with robust error variances.(18) In order to determine if the frailty status contributed information above and beyond that of the toxicity risk calculator previously reported from this cohort, we also adjusted the association of

frailty with outcomes, by risk group as determined by the calculator.(11) Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC). Bonferroni correction was used to correct for multiple testing for these five outcomes. All statistical tests were two-sided and p values less than 0.01 were considered statistically significant.

This study was approved by the Institutional Review Board of the City of Hope Comprehensive Cancer Center.

Results

Five hundred patients age 65 and older enrolled on this study (mean=73, SD=6.18): 35% of patients were ages 65 to 69, 46% from 70 through 79, and 19% 80 and above. Lung and GI cancers were the most prevalent with Breast, GYN, GU malignancies, and others also represented. The majority (61%) of patients had stage IV disease. Fifty–six percent of the patients were females, 20% with graduate school education, 41% with college education, 61% were married, 79% were living with a companion and 85% of the patients were white. (Table 2)

Two hundred and fifty (50%) of the patients were non-frail, 197 (39%) were pre-frail and 53 (11%) were frail. (Figure 1) The distribution of robust, pre-frail and frail did not differ by gender, race, and employment. However, non-frail (robust) patients tended to be younger than both pre-frail and frail patients. Compared to robust patients, pre-frail and frail patients were more likely to have lower education; more likely to be widowed/single/separated/divorced; more likely to be living alone, and with higher stage cancer. Stepwise multivariate multinomial logistic regression of the demographic characteristics retained age, education, living alone and cancer stage as significant variables associated with pre-frail and frail. Older patients (age 80+), patients with lower than high school education, patients living alone, and patients with higher stage (IV) cancer were more likely to be in the pre-frail and frail group (Table 3).

Table 4 shows the total number of outcome of events experienced by the study group. Both direct chemotherapy-related and patient-related outcomes were common. The most common was grade 3+ chemotherapy toxicity but hospitalizations and drug discontinuation occurred in over 15% of the patients. Although univariately, frail patients were more likely to have grade 3+ toxicity, after adjustment for toxicity risk group, the association became non-significant. Pre-frail or frail status were not associated with dose delay or dose reduction. Comparing frail and pre-frail to the robust group, frail patients were more likely to discontinue their chemotherapy (RR=2.06, 95%CI, 1.26–3.38, p=0.004) and more likely to be hospitalized (RR=1.98, 95%CI 1.26–3.11, p=0.003) even after adjustment for toxicity risk group.

Discussion

The increasing number of older patients with cancer seen by oncologists presents significant challenges in decision-making and care planning. This is due to multiple factors including comorbidities and functional status. Comprehensive Geriatric Assessment was developed in part to address this issue allowing for the collection of information from a broad array of

domains potentially impacting a patient's health status. Though the individual components of the CGA are needed to direct specific interventions, clinicians and investigators find having a summary measure useful for stratification and outcome prediction (19). Here we have demonstrated the feasibility of calculating a Deficit Accumulation Frailty Index derived from a largely self-administered Comprehensive Geriatric Assessment to provide such a measure and related it to relevant outcomes in older patients undergoing chemotherapy. To our knowledge, this is the first time such an index has been evaluated in older adults with cancer receiving chemotherapy. We show that both the states of pre-frailty and frailty are associated with grade 3+ toxicity. This relationship was attenuated when we controlled for toxicity risk as determined by the toxicity risk calculator previously reported by our group. (11) On the other hand other adverse patient outcomes such as discontinuation of therapy and subsequent hospitalization were associated with pre-frailty and frailty even after controlling for the toxicity risk calculator. This suggests that the DAFI is sensitive to patient related issues in addition to direct drug toxicity per se. Thus, the frailty index determined from a CGA provides a summary measure which could prove useful to oncologists who are increasingly seeking to use the concept of frailty to direct treatment decisions (20). Moreover as the CGA becomes available electronically the DAFI-CGA could potentially be calculated within the electronic health record with little effort from the clinician (21). While we use all items available from the CGA to calculate the index, it is possible that an index could be calculated from a more abbreviated CGA, but it would have to fulfill the criteria of having at least 30 items to be valid as previously reported (12–14).

Frailty in a sense is a summary measure of the impacts of aging and disease on a patient's health status and has been shown to represent a state of vulnerability and risk for adverse outcomes.(4) Two major approaches to the categorization of frailty have evolved over the years.(4) One is a phenotype measure developed initially by the Johns Hopkins group, which relies on specific items to be present in order to characterize the frailty state. The Deficit Accumulation Index approach popularized by Rockwood and colleagues, and others, takes the approach that if one collects information on a substantial number of varying aspects of one's health status, a determination of the fraction of those items incurred by a given patient creates a scalable Frailty Index.(4,12,14) Such an index has been shown in many studies to identify degrees of frailty which then correlate with a variety of health outcomes, with mortality the most frequently reported.(4,13,16,17) Thus, the spectrum of the DAFI scores reflects the biological age of individuals taking into account physiologic as well as disease related changes. At the lower end of the scale, it reflects a state of robustness and potential resilience while at the upper end it reflects a state of frailty and vulnerability.

The deficit accumulation approach can be applied to any dataset as long as it contains enough varied items. Song et. al have determined that if one has at least 30 items a Frailty Index can be calculated.(15) Moreover a number of studies have shown that regardless of which items are included, there is a remarkable similarity of the points at which pre-frailty and frailty appear.(4,22,23) The Frailty Index was initially operationalized from a CGA by Jones et al and a standard procedure for creating a Frailty Index as described by Searle et al in 2008 (12,14), and shown to predict the risk of death, length of stay, and discharge to long term care in hospitalized older patients.(13)

A formal Deficit Accumulation Frailty Index has not previously been applied to older cancer patients receiving chemotherapy.(19) We previously reported that an index derived from data other than a CGA can predict initiation or non-initiation of adjuvant hormonal therapy in older women with breast cancer.(16) The frailty distribution of the subjects reported here showed fewer patients in the robust category and more in the pre-frail and frail categories than in that study, perhaps reflecting the presence of more active disease or later stage in our cohort. The frequency of frailty and pre-frailty in our older cancer patients is similar to, but slightly lower than, that reported for community dwelling older adults.(15,24) This may reflect a selection bias in choosing the healthiest appearing patients for treatment since our level of frailty is substantially lower than that reported for hospitalized older patients (13,24). It thus appears that this approach can provide important summary information for clinicians as they ponder difficult choices. The DAFI-CGA was associated with direct chemotherapy toxicity related outcomes such as grade 3+ toxicity. This association was attenuated after controlling for the risk stratification scheme previously developed from this CGA data, specifically for the purpose of chemotherapy toxicity identification.(11) However the DAFI-CGA was independently associated with discontinuation of therapy, perhaps because discontinuation may relate to issues other than grade 3+ toxicity per se. This could include an inability to tolerate lower levels of toxicity or how the patient reacts to or tolerates a given level of toxicity. For a more frail person that threshold may be lower for both the patient and physician, resulting in discontinuation. Moreover, the DAFI-CGA was strongly associated with what might be called a more general geriatric phenomenon (i.e. hospitalization). Thus the DAFI-CGA as a single measure is associated with both direct chemotherapy and other important outcomes of treatment. Outcomes, such as treatment discontinuation or hospitalizations, may be related to an accumulation of physiologic and functional deficits, which are distinct from the factors associated with chemotherapy toxicity risk. The determination that a patient is frail or pre-frail might target such patients as needing more assistance and/or perhaps pre-chemotherapy treatment directed at these declines such as attention to comorbidities, exercise, and physical therapy to avoid falls.

Limitations to this study include that: it reports only grade 3+ toxicity, while as indicated above lower levels of toxicity may be of importance to older patients; our subjects included those with various tumor types and stages of disease; and laboratory abnormalities were not included in the index and possibility might further enhance its utility.

Nevertheless the DAFI CGA appears to have clinically useful potential since it provides a summary indicator of vulnerabilities in older individuals which likely is the aggregate result of a decrease in reserve capacity of a number of systems.(1,4). Moreover, since the self-administered CGA has been shown to be feasible (less than 30 minutes, of which all but 5 minutes are patient self-reported) (9,10) and is now being used more widely in clinical trials and in practice (25,26), using a DAFI-CGA may be a good way to stratify patients for studies and potentially even to select patients who may require targeted geriatrics interventions to enhance the outcomes from the specific therapy. Since we know that hospitalizations are often predictive of subsequent poor outcomes including mortality, the determination of the DAFI-CGA may assist oncologists in identifying patients at risk for such events and alerting them to seek further assistance, e.g. geriatrics consultation, in the care of such individuals.(24) Of course, validation of the DAFI-CGA approach in an

independent cohort, and prospective trials of its relationship to these and other outcomes will be needed to fully establish its role.

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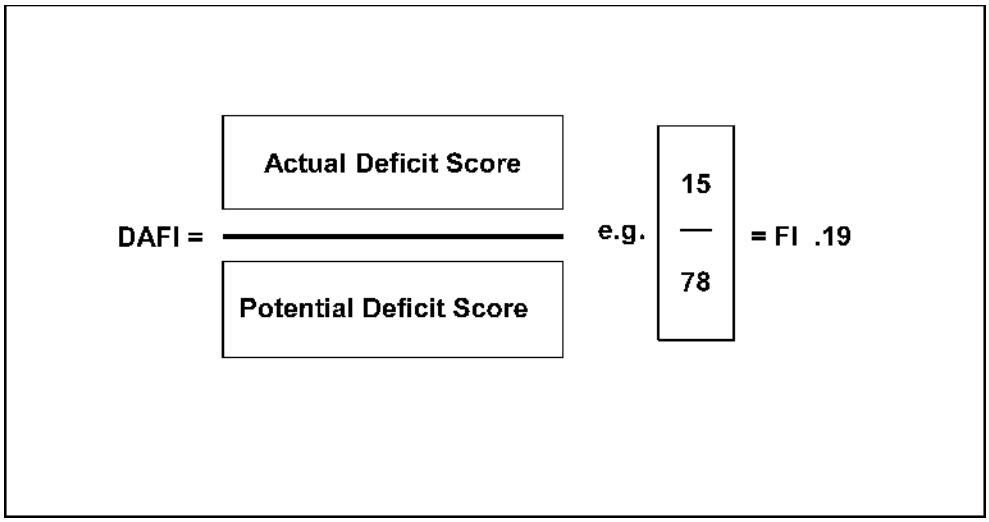

Figure 1.
Calculation of the Frailty Index. The potential score ranges from 0 to 1.0

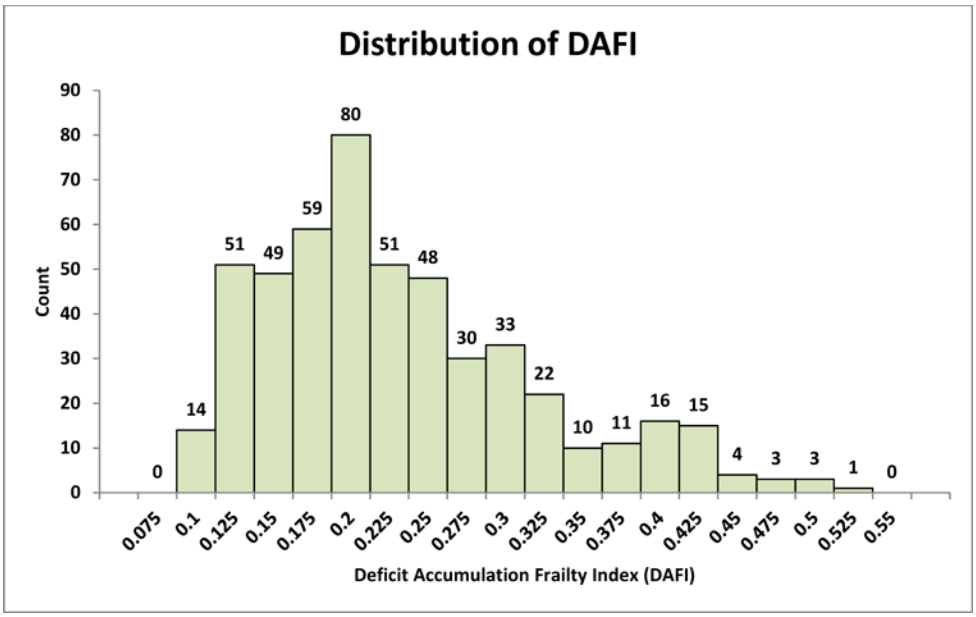

Figure 2.
Distribution of Frailty Scores in the CARG cohort

Table 1

Geriatric Assessment Items for Frailty Index

Item	Item	No Frailty (+0)	+1 Frailty Risk	+2 Frailty Risk
Demographics				
1	Marital Status	Married	All others (single, divorced, separated)	
Instrumental Activities of Daily Living				
2	Telephone	Without help	Need at least some help	
3	Travel	Without help	Need at least some help	
4	Shopping	Without help	Need at least some help	
5	Prepare meals	Without help	Need at least some help	
6	Housework	Without help	Need at least some help	
7	Take medicines	Without help	Need at least some help	
8	Handle money	Without help	Need at least some help	
Activities of Daily Living				
9	Lifting groceries	Not limited	Limited a little/Limited a lot	
10	Climbing 1 flight of stairs	Not limited	Limited a little/Limited a lot	
11	Bending kneeling	Not limited	Limited a little/Limited a lot	
12	Walking >1 blocks	Not limited	Limited a little	Limited a lot
13	Walking 1 block	Not limited	Limited a little	Limited a lot
14	Bathing/dressing	Not limited	Limited a little	Limited a lot
Patient-Rated KPS				
15	Normal activity	Normal/minor sympt (100−90)	Effort/some symptoms (80)	Unable/disabled (≤70)
No. of Falls				
16	Falls	0–1 fall	2+ falls	
Polypharmacy				
17	Meds taken daily	<5	>= 5	
Comorbidity				
18	Other cancer/leuk	Present: No	Present: Yes	If great deal of impact
19	Arthritis	Present: No	Present: Yes	If great deal of impact
20	Glaucoma	Present: No	Present: Yes	If great deal of impact
21	Emphysem/bronch	Present: No	Present: Yes	If great deal of impact
22	High blood press	Present: No	Present: Yes	If great deal of impact
23	Heart Disease	Present: No	Present: Yes	If great deal of impact
24	Circulation trouble	Present: No	Present: Yes	If great deal of impact
25	Diabetes	Present: No	Present: Yes	If great deal of impact
26	Stomach GI	Present: No	Present: Yes	If great deal of impact
27	Osteoporosis	Present: No	Present: Yes	If great deal of impact
28	Liver/kidney	Present: No	Present: Yes	If great deal of impact
29	Stroke	Present: No	Present: Yes	If great deal of impact

Item	Item	No Frailty (+0)	+1 Frailty Risk	+2 Frailty Risk
30	Depression	Present: No	Present: Yes	If great deal of impact
31	Eyesight	Excellent Good	Fair/Poor/Blind	If great deal of impact
32	Hearing	Excellent Good	Fair/Poor/Blind	If great deal of impact
Nutritional Status				
33	Weight loss	No	Yes (≥5%)	
Psychosocial Status				
34	HADS: Depression score	<11	>=11	
35	HADS: Anxiety score	<11	>=11	
36	HADS Total Score	<15	≥ 15	
37	Social activity over the past 4 weeks	No interference in activities	Some interference in activities (most of the time to a little of the time)	Always interference in activities (All of the time)
38	Change in social activity over past 6 months	At least as active	Less active	
39	Comparison of social activity level to others their age	Same or less limited vs peers	More limited vs peers	
Social Support				
40	Confined to bed	Someone all the time	Someone sometime	No one
41	Take to MD	Someone all the time	Someone sometime	No one
42	Prepare meals	Someone all the time	Someone sometime	No one
43	Daily chores	Someone all the time	Someone sometime	No one
Health-Care Professional Questionnaire				
Functional Status				
44	MD-Rated KPS	90–100	80	0–70
45	Time to up and go	< 13	>= 13	
Cognition				
46	Cogn/Memory	0–10.99	>= 11	
Nutritional Status				
47	BMI	18.5–24.99	< 18.5 or >= 25	
Labs				
48	Creatinine clearance	≥ 60 mL/min	30–59 mL/min	<30 mL/min
49	Hemoglobin	Normal	Abnormal [<12 g/dl (female), <13 g/dl (male)]	
50	Albumin	Normal	Abnormal (< 3.5)	
51	LFT	Normal	Abnormal	

Table 2

Demographic and clinical characteristics and frailty

	Overall	Robust	Pre-Frail	Frail	P value
Sex					0.3093
Female	281 (56.2%)	134 (53.6%)	119 (60.4%)	28 (52.8%)	
Male	219 (43.8%)	116 (46.4%)	78 (39.6%)	25 (47.2%)	
Age					0.0006
65–69	175 (35.0%)	96 (38.4%)	59 (30.0%)	20 (37.7%)	
70–74	127 (25.4%)	71 (28.4%)	49 (24.9%)	7 (13.2%)	
75–79	105 (21.0%)	56 (22.4%)	37 (18.7%)	12 (22.6%)	
80+	93 (18.6%)	27 (10.8%)	52 (26.4%)	14 (26.4%)	
Race					0.5966
White	426 (85.2%)	217 (86.8%)	165 (83.8%)	44 (83%)	
others	74 (14.8%)	33 (13.2%)	32 (16.2%)	9 (17%)	
Education					0.0379
Missing	1	1 (.%)	0 (.%)	0 (.%)	
<=High school	193 (38.7%)	82 (32.9%)	82 (41.6%)	29 (54.7%)	
college	202 (40.5%)	110 (44.2%)	75 (38.1%)	17 (32.1%)	
Graduate school	104 (20.8%)	57 (22.9%)	40 (20.3%)	7 (13.2%)	
Marital status					0.002
Married	306 (61.2%)	175 (70%)	103 (52.3%)	28 (52.8%)	
Widowed	113 (22.6%)	41 (16.4%)	57 (28.9%)	15 (28.3%)	
Single/rest	81 (16.2%)	34 (13.6%)	37 (18.8%)	10 (18.9%)	
Living alone					0.0007
Missing	3	0 (.%)	2 (.%)	1 (.%)	
Yes	106 (21.3%)	36 (14.4%)	55 (28.2%)	15 (28.8%)	
No	391 (78.7%)	214 (85.6%)	140 (71.8%)	37 (71.2%)	
Employment					0.1134
Employed	395 (79%)	188 (75.2%)	163 (82.7%)	44 (83%)	
The rest	105 (21%)	62 (24.8%)	34 (17.3%)	9 (17%)	

	Overall	Robust	Pre-Frail	Frail	P value
Cancer type					0.08
Lung	143 (28.6%)	58 (23.2%)	64 (32.5%)	21 (39.6%)	
GI	135 (27.0%)	69 (27.6%)	49 (24.9%)	17 (32.1%)	
Breast/GYN	144 (28.8%)	79 (31.6%)	55 (27.9%)	10 (18.9%)	
GU/others	78 (15.6%)	44 (17.6%)	29 (14.7%)	5 (9.4%)	
Caner Stage					0.0005
I/II	82 (16.5%)	53 (21.4%)	21 (10.7%)	8 (15.1%)	
III	109 (21.9%)	64 (25.8%)	40 (20.3%)	5 (9.4%)	
IV	307 (61.7%)	131 (52.8%)	136 (69.0%)	40 (75.5%)	

Abbreviations: GU, genitourinary; GYN, gynecologic.

Table 3

Factors associated with pre-frail and frail

		OR (95%CI) for	
	Robust	**Pre-Frail**	**Frail**
Age			
65–79	1.00		
80+		2.68(1.58–4.54)	2.78(1.31–5.93)
		0.0003	0.008
Education			
College/graduate school	1.00		
<=High school		1.48(0.99–2.22)	2.38(1.28–4.43)
		0.06	0.006
Living alone			
No	1.00		
Yes		2.34(1.43–3.82)	2.47(1.20–5.08)
Caner Stage		0.0007	0.01
I/II/III	1.00		
IV		2.09(1.39–3.15)	3.11(1.54–6.29)
		0.0004	0.002

Table 4

The associations between Pre-frail/Frail and grade 3+ toxicity, dose reduction, dose delay, discontinuation and hospitalization

Outcomes	Robust	Pre-Frail	Frail
	250 (50%)	197 (39%)	53 (11%)
	N (col%)	N (col%)	N (col%)
Toxicity Grade 3+			
No	124 (50%)	93 (47%)	17 (32%)
Yes	126 (50%)	104 (53%)	36 (68%)
Univariate RR (95%I)	1.00	1.04 (0.87–1.25)	1.34 (1.08–1.68)
Univariate P value		0.61	0.009
Adjusted RR		0.85 (0.71–1.02)	0.96 (0.75–1.21)
Adjusted P value		0.09	0.71
Dose Reductions			
No	173 (69%)	139 (71%)	35 (66%)
Yes	77 (31%)	58 (29%)	18 (34%)
Univariate RR (95%I)	1.00	0.96 (0.72–1.27)	1.10 (0.73–1.68)
Univariate P value		0.65	0.68
Adjusted RR		0.81 (0.61–1.09)	0.88 (0.57–1.34)
Adjusted P value		0.16	0.54
Dose Delays			
No	180 (72%)	127 (64%)	38 (72%)
Yes	70 (28%)	70 (36%)	15 (28%)
Univariate RR (95%I)	1.00	1.27 (0.97–1.67)	1.01 (0.63–1.62)
Univariate P value		0.09	0.96
Adjusted RR		1.02 (0.76–1.35)	0.72 (0.45–1.16)
Adjusted P value		0.91	0.18
Discontinuation			
No	209 (84%)	152 (77%)	33 (62%)
Yes	41 (16%)	45 (23%)	20 (38%)
Univariate RR (95%I)	1.00	1.39 (0.95–2.04)	2.30 (1.47–3.59)
Univariate P value		0.09	0.0002
Adjusted RR		1.28 (0.86–1.91)	2.06 (1.26–3.38)
Adjusted P value		0.23	0.004
Hospitalization			
No	206 (82%)	149 (76%)	29 (55%)
Yes	44 (18%)	48 (24%)	24 (45%)
Univariate RR (95%I)	1.00	1.38 (0.96–1.99)	2.68 (1.81–3.96)
Univariate P value		0.08	<0.001
Adjusted RR		1.20 (0.82–1.76)	1.98 (1.26–3.11)

Outcomes	Robust	Pre-Frail	Frail
Adjusted P value		0.36	0.003

Adjusted RR: adjusted for risk group (low middle high). *36 patients with missing risk group were not included.