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Geriatric Oncology

Association of Pre-Chemotherapy Peripheral Blood Pro-Inflammatory and Coagulation Factors with Physical Function in Women with Breast Cancer

Yuan Yuan,[a] Nilesh Vora,[b] Can-Lan Sun,[a] Daneng Li,[a] David Smith,[a] Joanne Mortimer,[a] The-Hang Luu,[a] George Somlo,[a] James Waisman,[a] Joseph Chao,[a] Vani Katheria,[a] Timothy Synold,[a] Vivi Tran,[a] Shu Mi,[a] Tao Feng,[a] Abrahm Levi,[a] Anait Arsenyan,[a] Jennifer Choi,[a] Laura Zavala,[a] Susan Yost,[a] Arti Hurria[a]

[a]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, California, USA; [b]Long Beach Memorial Medical Center, Long Beach, California, USA

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

Key Words. Breast cancer • Aging biomarkers • Physical function • Chemotherapy

Abstract

Background. Pro-inflammatory and coagulation factors serve as biomarkers of aging and functional reserve. The purpose of this study was to determine if pro-inflammatory (interleukin-6 [IL-6], C-reactive protein [CRP]), and coagulation (D-dimer) factors were associated with pre-chemotherapy functional status in women with stage I–III breast cancer.

Patients and Methods. Prior to chemotherapy initiation in patients with stage I–III breast cancer, the following was captured: IL-6, CRP, D-dimer blood levels, and physical function measures including activities of daily living (ADL, subscale of Medical Outcomes Study Physical Health); instrumental activities of daily living (IADL, subscale of the Older Americans Resources and Services Program); Timed Up and Go (TUG); physician-rated Karnofsky Performance Status (KPS); and self-rated KPS. The association of these biomarkers with physical function measures was evaluated.

Results. One hundred sixty patients (mean age 58.3 years, range 30–81 years) with stage I–III breast cancer (stages I [$n = 34$; 21.5%], II [$n = 88$; 55.7%], III [$n = 36$; 22.8%]) were enrolled. The group with poorest physical function (defined by ADL <70, IADL <14, and TUG ≥10 seconds) had higher levels of IL-6 ($p = .05$), D-dimer ($p = .0004$), and CRP ($p = .05$). There was no significant association between these biomarkers and KPS. Patients with at least two biomarkers in the highest quartile were more likely to have poorer physical function (odds ration [OR] 18.75, $p < .001$). In multivariate analysis adjusting for age, stage, number of comorbidities, and body mass index, the association remained (OR 14.6, $p = .002$).

Conclusion. Pre-chemotherapy biomarkers of aging are associated with poorer physical function among patients with breast cancer across the aging spectrum. ***The Oncologist*** 2017;22:1189–1196

Implications for Practice: Commonly used physical function assessment tools may not reflect the diverse nature of physical function and risk for chemotherapy toxicity, particularly in older adults. No laboratory test reflects functional reserve. Pro-inflammatory and coagulation factors, such as IL-6, CRP, and D-dimer, can serve as biomarkers of aging and physical function; however, few studies have evaluated their utility in patients with cancer. This study was designed to understand the association between pre-chemotherapy biomarkers and physical function in women with early stage breast cancer undergoing adjuvant chemotherapy. Results indicate that elevated pre-chemotherapy levels in two of the three peripheral biomarkers are associated with the poorest physical function among patients with breast cancer across the aging spectrum.

Introduction

Breast cancer is a disease associated with aging, with the median age of diagnosis at 62 in the U.S. [1, 2]. Most patients will be diagnosed with early-stage disease, necessitating multimodality therapy including chemotherapy. However, this therapy comes at a risk of toxicity, functional decline, and, rarely, treatment-related mortality [3–5]. Prior to initiation of chemotherapy, an assessment of functional reserve is needed. In standard oncology practice, the Karnofsky performance status (KPS) or Eastern Cooperative Oncology Group score is captured as a one-item assessment of physical function. However, prior research has demonstrated that these simple assessments of performance status may not reflect the diverse nature of

Correspondence: Yuan Yuan, M.D., City of Hope Comprehensive Cancer Center and Beckman Research Institute, 1500 East Duarte Road, Duarte, California 91010, USA. Telephone: 626-256-4673; e-mail: yuyuan@coh.org Received October 7, 2016; accepted for publication April 11, 2017; published Online First on May 30, 2017. http://dx.doi.org/10.1634/theoncologist.2016-0391

Table 1. Patient characteristics ($n = 160$)

Baseline characteristic	*n* (%)
Age, median (range)	58.5 (30–81)
<50	39 (24.4%)
50–<60	44 (27.5%)
60–<70	46 (28.8%)
≥70	31 (19.4%)
Race	
Non-Hispanic white	80 (50.3%)
Hispanics	41 (25.8%)
Black	17 (10.7%)
Asian	15 (9.4%)
Others	6 (3.8%)
Missing	1
Breast cancer stage	
I	35 (21.9%)
II	88 (55.0%)
III	37 (23.1%)
ER, PR, HER2 status	
ER+ or PR+, HER2−	107 (66.9%)
HER2+	25 (15.6%)
ER-PR-HER2−	28 (17.5%)
Type of Chemotherapy	
Neoadjuvant	17 (10.6%)
Adjuvant	143 (89.4%)
Comorbidities	
Hypertension	54 (33.8%)
Arthritis	47 (29.4%)
Depression	31 (19.4%)
Circulation problem	22 (13.8%)
Other cancers	18 (11.3%)
Stomach disorders	17 (10.6%)
Other[a]	44 (27.7%)
Comorbidities ≥1	105 (65.6%)
Comorbidities ≥2	64 (40.0%)
Comorbidities ≥3	35 (21.9%)

[a]Other comorbidities include: heart disease (15, 9.4%), diabetes (12, 7.5%), glaucoma (9, 5.6%), emphysema (5, 3.1%), liver/kidney disease (2, 1.3%), and stroke (1, 0.6%).

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HER2−, human epidermal growth receptor 2 negative; HER2+, human epidermal growth receptor 2 positive; PR, progesterone receptor.

physical function and risk of chemotherapy toxicity, particularly among older adults. Furthermore, there is no laboratory test to reflect an individual's functional reserve. The goal of this study was to determine whether peripheral blood biomarkers of aging are associated with measures of physical function among patients with breast cancer who are scheduled to receive adjuvant or neoadjuvant chemotherapy.

In the geriatric literature, markers of inflammation, such as interleukin-6 (IL-6) [6], C-reactive protein (CRP) [7, 8], and coagulation factor (D-dimer) [9], are increasingly being recognized as potential biomarkers of aging, given their association with functional decline and increased mortality in older adults. At a research conference held by the National Institute of Aging, it was hypothesized that markers of inflammation and coagulation were part of the underlying pathway to frailty [10, 11]. The role of these biomarkers in the oncology population has not been widely studied. The rationale for studying these in the oncology population is to identify a method of assessing functional reserve, which is particularly important when considering the risks of chemotherapy because chronological age alone is a poor predictor of chemotherapy tolerance. Based on the growing evidence for the utility of markers of inflammation and coagulation in the geriatric literature, we hypothesized that IL-6, CRP, and D-dimer may serve as markers of physical function reserve among patients with breast cancer. The primary goal of this study was to understand the association between pre-chemotherapy biomarkers (IL-6, CRP, and D-dimer) and physical function.

Table 2. Distribution of the measures of physical function (ADL, IADL, TUG, patient KPS, physician KPS) and peripheral blood biomarkers (IL-6, CRP, and D-dimer)

Domains	Mean (SD)	Median (Range)	Q1, Q3
ADL (MOS physical health)	79.5 (22.6)	90 (0–100)	70, 95
IADL (subscale of OARS)	12.3 (2.85)	14 (4–14)	12, 14
Patient self-rated KPS	89.9 (13.2)	90 (50–100)	90, 100
Physician-rated KPS	94.7 (5.84)	100 (80–100)	90, 100
TUG	9.7 (2.21)	9.5 (5–18)	
IL-6 (pg/mL)	3.4 (4.8)	1.9 (0–42.1)	0.3, 4.9
CRP (μg/mL)	5.5 (7.8)	2.8 (0.1–48.4)	1.4, 6.0
D-dimer (μg/mL)	0.8 (0.59)	0.6 (0.1–3.3)	0.4, 1.1

Abbreviations: ADL, activities of daily living; CRP, C-reactive protein; IADL, instrumental activities of daily living; IL-6, interleukin-6; KPS, Karnofsky performance status; MOS, medical outcome study physical heath scale; OARS, Older Americans Resources and Services Program; Q1, the first quartile cut off (25%); Q3, the third quartile cut off (75%); TUG, Timed Up and Go.

Materials and Methods

Eligible patients had stage I–III breast cancer, were scheduled to receive adjuvant or neoadjuvant chemotherapy, and were able to understand English and provide informed consent. Patients with metastatic disease were excluded. The primary objective of the overall study was to evaluate longitudinal changes in functional status in patients with stage I–III breast cancer receiving adjuvant or neoadjuvant chemotherapy. A secondary objective was to understand the association between pre-chemotherapy biomarkers of aging and physical function. The study was approved by the institutional review boards of the participating institutions (City of Hope and Long Beach Memorial Medical Center). Participating patients completed the informed consent process.

Study Schema

At study entry, the health care team captured sociodemographic information (including age and race), breast cancer pathology features (stage, hormone receptors [estrogen receptor (ER), progesterone receptor (PR)], and HER2 status), and chemotherapy treatment variables (regimen and dosing).

Table 3. Distribution of peripheral blood biomarkers as continuous variables by categorized physical function measures

	IL-6 (pg/mL)			D-dimer (μg/mL)			CRP (μg/mL)		
Physical function measures	**Mean (SD)**	**Median (range)**	***p***	**Mean (SD)**	**Median (range)**	***p***	**Mean (SD)**	**Median (range)**	***p***
ADL (MOS physical health)									
<70 (*n* = 38)	5.5 (7.89)	2.4 (0.0–42.1)	.27	1.0 (0.74)	1.0 (0.1–3.3)	.02	6.7 (9.19)	3.5 (0.2–48.4)	.27
≥70 (*n* = 122)	2.7 (3.08)	1.7 (0.0–18.4)		0.7 (0.52)	0.6 (0.1–3.2)		5.2 (7.31)	2.6 (0.1–44.3)	
IADL									
<14 (*n* = 61)	4.7 (6.52)	2.5 (0.0–42.1)	.07	0.9 (0.65)	0.7 (0.1–3.3)	.13	6.2 (8.68)	2.7 (0.3–48.4)	.63
14 (*n* = 99)	2.6 (3.12)	1.5 (0.0–18.4)		0.7 (0.55)	0.6 (0.1–3.2)		5.1 (7.20)	2.9 (0.1–44.3)	
TUG									
≥10 (*n* = 55)	5.0 (6.78)	2.7 (0.0–42.1)	.07	0.9 (0.67)	0.8 (0.1–3.3)	.03	6.1 (8.04)	3.1 (1.0–48.4)	.24
<10 (*n* = 101)	2.5 (3.09)	1.5 (0.0–18.4)		0.7 (0.51)	0.5 (0.1–3.2)		5.3 (7.79)	2.6 (0.1–44.3)	
Poorest physical function group[a] vs. others									
0 (*n* = 18)	8.8 (10.15)	7.2 (0.0–42.1)	.05	1.3 (0.83)	1.1 (0.1–3.3)	.0004	10.4 (12.13)	5.9 (1.2–48.4)	.05
1 (*n* = 142)	2.7 (3.09)	1.7 (0.0–18.4)		0.7 (0.52)	0.6 (0.1–3.2)		4.9 (6.88)	2.6 (0.1–44.3)	
Patient self-rated KPS									
<90 (*n* = 39)	4.3 (4.50)	2.5 (0.0–19.6)	.10	1.0 (0.72)	0.7 (0.1–3.3)	.18	4.9 (5.98)	2.7 (0.2–29.4)	.58
90 and 100 (*n* = 121)	3.1 (4.89)	1.6 (0.0–42.1)		0.7 (0.53)	0.6 (0.1–3.2)		5.7 (8.30)	2.8 (0.1–48.4)	
Physician-rated KPS									
<90 (*n* = 7)	6.5 (5.60)	9.0 (0.0–13.7)	.70	1.1 (0.58)	1.0 (0.4–1.9)	.05	10.7 (16.89)	4.8 (0.4–48.4)	.25
90 and 100 (*n* = 149)	3.3 (4.79)	1.9 (0.0–42.1)		0.8 (0.59)	0.6 (0.1–3.3)		5.3 (7.20)	2.6 (0.1–44.3)	

[a]Poorest physical function group is represented by 0, which is a combination of ADL score of <70, IADL score of <14, and TUG of ≥10 seconds. 1 = all others.

Abbreviations: ADL, activities of daily living; CRP, C-reactive protein; IADL, instrumental activities of daily living; IL-6, interleukin-6; KPS, Karnofsky performance status; MOS, medical outcome study; TUG, Timed Up and Go.

All patients completed a questionnaire that included measures of functional status, comorbidities, and weight/height (utilized to calculate body mass index). Measures of functional status included:

- Activities of Daily Living (ADL) measured by the Medical Outcome Study (MOS) Physical Heath scale: This scale evaluated a range of activities from ability to bathe to ability to run. Functional status is rated on a scale of 0–100 with a higher score indicating better physical function.
- Instrumental Activities of Daily Living (IADL) scale: This scale measures the ability to complete activities that are required for independence in the community, such as shopping and taking transportation. Functional status is rated on a scale of 0–14 with a higher score signifying greater independence.
- Physician-rated KPS: This is a one item global measure of performance status measured on a scale of 0–100 with a higher score reflecting better function.
- Patient self-rated KPS: This is a one item global measure of performance status that the patient self-rates from a scale of 40–100.
- Timed Up and Go (TUG): The performance based measure of functional status measures the time that it takes (in seconds) to rise from a chair, walk 3 feet, turn around, walk back to the chair, and sit down.

Comorbidity was evaluated using the Older Americans Resources and Services Program (OARS) questionnaire [12] in which patients respond to whether they have the following comorbidities (yes/no) to 13 comorbidities, such as hypertension, arthritis, diabetes, heart disease, and stroke. Each of these comorbidities has been associated with increased levels of IL-6, D-dimer, and/or CRP [6, 7, 9, 13].

At time of enrollment, an optional blood specimen (7.5 mL) was collected pre-chemotherapy for measurement of pro-inflammatory (IL-6 and CRP) and coagulation (D-dimer) factors. Plasma was stored at −80°C until assays were run. Quantitative IL-6 and CRP levels were measured using human IL6 ELISA Kit (Invitrogen) and D-dimer levels were measured using Nanopia® D-dimer kit (Sekisui Medical Co.)

Between July 2009 and December 2014, 206 patients were accrued. The current analysis included 160 patients who consented for the pre-chemotherapy blood sample for biomarker measurements. There was no difference between the 160 patients who contributed and 46 who declined blood sample in terms of age, race/ethnicity, disease stage, hormonal receptor status, and functional status.

Statistical Analyses

Descriptive statistics were performed to summarize patient, tumor, treatment characteristics, and physical function measures. Mean (SD) and median (inter-quartiles) were calculated for peripheral blood biomarkers (IL-6, CRP, and D-dimer) and physical function measures (ADL, IADL, TUG, patient self-rated KPS, and physician-rated KPS). Categorical variables for peripheral blood biomarkers were created using the median (≥median, <median) and the third quartile as cutoff points (quartile four vs. quartiles one to three). Each functional status

Table 4. Association of prechemotherapy biomarkers of aging and breast cancer stage, age, comorbidity

Patient Characteristics	IL-6 (pg/mL)	CRP (μg/mL)	D-dimer (μg/mL)
Stage	Median, $p < .0001$	Median, $p = .80$	Median, $p = .43$
I	0.1	2.6	0.5
II	2.1	2.9	0.6
III	3.9	2.5	0.6
Age	Median, $p = 1.0$	Median, $p = .56$	Median, $p = .05$
<50	1.9	3.0	0.4
50–59	1.7	2.5	0.6
60–69	1.8	2.9	0.7
≥70	1.7	3.0	0.9
Neoadjuvant	4.1, $p = .06$	5.5, $p = .62$	0.7, $p = .17$
Adjuvant	1.7	2.7	0.6
Comorbidity			
≤1	2.1, $p = .33$	2.8, $p = .75$	0.5, $p < .001$
≥2	1.6	2.7	1.0

Abbreviations: CRP, C-reactive protein; IL-6, interleukin-6.

variable was dichotomized with "0" indicating poor physical function and "1" indicating good physical function: ADL (0 = ADL <70; 1 = ADL 70–100), IADL (0 = IADL <14; 1 = IADL 14), TUG (0 = TUG >10 seconds; 1 = TUG ≤10 seconds), patient self-rated KPS (0 = KPS <90; 1 = KPS 90 or 100), physician-rated KPS (0 = KPS <90; 1 = KPS 90 or 100). For ADL (MOS Physical), a score of 70 or lower represents the poorest quartile of physical function. For IADL, 14 represents independence. Finally, we identified a group with poorest physical function (defined as ADL <70, IADL <14, and TUG >10 seconds).

A Pearson product-moment correlation coefficient was computed to assess the relationship among the peripheral blood biomarkers. The values of the peripheral blood biomarkers (IL-6, CRP, and D-dimer) were not normally distributed. Mood's median test was used to compare the medians of the biomarkers across the physical function measures. Logistic regression was used to examine the relationships between each individual biomarker and each physical function measure, as well as the group with the poorest physical function described above. The association between the peripheral blood biomarkers and clinical variables (comorbidities, disease stage, and hormonal receptor status) were analyzed using logistic regression treating dichotomized biomarkers as independent variables. The variable was included in the multivariate analyses if the p value was < .10. Age and body mass index (BMI) were kept in the multivariate model regardless of their p values. All statistical tests were two-sided and p values less than .05 were considered statistically significant. Data were analyzed using SAS 9.3 (analytic software; SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html).

Results

Patient, Tumor, and Treatment Characteristics

The mean age of patients ($n = 160$) was 58.3 years (SD, 11.7; range, 30–81years) with stage I ($n = 35$, 21.9%), II ($n = 88$,

Table 5. Univariate association between dichotomized peripheral blood biomarkers and categorized physical function assessment

	ADL (MOS physical health)			IADL			TUG			Poorest physical function group[b]		
Biomarkers	No. Pt ≥70 vs. <70	OR (95% CI)	p	No. Pt 14 vs. <14	OR (95% CI)	p	No. Pt <10 vs ≥10	OR (95% CI)	p	No. Pt 123/0	OR (95% CI)	p
IL-6 (pg/mL)												
<5	97/24	1.00		81/40	1.00		82/37	1.00		113/8	1.00	
≥5	25/14	2.26 (1.02, 5.00)	.04	18/21	2.36 (1.13, 4.93)	.02	19/18	2.10 (0.99, 4.46)	.05	29/10	4.87 (1.76, 13.44)	.002
D-dimer (μg/mL)												
<1	96/20	1.00		76/45	1.00		79/34	1.00		109/7	1.00	
≥1	25/18	3.46 (1.59, 7.49)	.002	23/16	1.59 (0.78, 3.24)	.20	21/21	2.32 (1.12, 4.80)	.02	32/11	5.35 (1.92, 14.94)	.001
CRP (μg/mL)												
<6	95/26	1.00		75/41	1.00		76/42	1.00		112/9	1.00	
≥6	27/12	1.62 (0.73, 3.64)	.24	23/20	1.17 (0.56, 2.46)	.67	25/13	0.94 (0.44, 2.03)	.88	30/9	3.73 (1.36, 10.23)	.01
Combined biomarkers[a]												
0	65/12	1.00		50/27	1.00		53/23	1.00		75/2	1.00	
1	38/12	1.71 (0.70–4.19)	0.24	35/15	0.79 (0.37–1.71)	.55	32/16	1.15 (0.53–2.50)	.72	45/5	4.17 (0.78–23.37)	.10
2 or 3	19/14	3.99 (1.58–10.07)	0.003	14/19	2.51 (1.09–5.79)	.03	16/16	2.30 (0.99–5.38)	.05	22/11	18.75 (3.86–91.00)	<.001

[a]Combined biomarkers: 0 = all three markers in lower three quartiles, 1 = 1 of the markers in the fourth quartile, 2 = 2 of the markers in the fourth quartile, 3 = all three markers in the fourth quartile.

[b]Poorest physical function group: combination of ADL score of <70, IADL score of <14, and TUG of ≥10 seconds; 0 = all three functions are poor (physically vulnerable), 1 = all others.

Abbreviations: ADL, activities of daily living; CI, confidence interval; CRP, C-reactive protein; IADL, instrumental activities of daily living; IL-6, interleukin-6; MOS, medical outcome study; OR, odds ratio; Pt, patient; TUG, Timed Up and Go.

Table 6. Multivariate association between peripheral blood biomarkers and categorized physical function assessment

	ADL (MOS physical health)		IADL		TUG		Poorest physical function group[b]	
Biomarkers	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
IL-6 (pg/mL)								
<5	1.00		1.00		1.00		1.00	
≥5	1.63 (0.65–4.08)	.30	2.10 (0.92–4.83)	.08	1.81 (0.73–4.47)	.20	3.67 (1.10–12.23)	.03
CRP (μg/mL)								
<6	1.00		1.00		1.00		1.00	
≥6	1.57 (0.60–4.16)	.36	0.83 (0.36–1.93)	.66	0.69 (0.27–1.76)	.44	5.75 (1.46–22.54)	.01
D-dimer (μg/mL)								
<1	1.00		1.00		1.00		3.22 (0.97–10.74)	
≥1	1.93 (0.80–4.64)	.14	1.24 (0.55–2.83)	.61	1.56 (0.65–3.47)	.32		.06
Combination biomarkers[a]								
0	1.00		1.00		1.00		1.00	
1	0.94 (0.35–2.54)	.91	0.55 (0.23–1.28)	.16	0.66 (0.27–1.59)	.35	2.46 (0.42–14.30)	.32
2 or 3	2.55 (0.91–7.10)	.07	1.80 (0.73–4.48)	.20	1.43 (0.54–3.78)	.47	14.70 (2.74–78.89)	.002

OR for each biomarker was adjusted for each other and age, BMI, number of comorbidities (≥2 vs. 1 or none), and stage of breast cancer.
[a]Combination biomarkers: 0 = all three markers in lower three quartiles, 1 = 1 of the markers in the fourth quartile, 2 = 2 of the markers in the fourth quartile, 3 = all three markers in the fourth quartile.
[b]Poorest physical function group: combination of ADL score of <70, IADL score of <14, and TUG of ≥10 seconds; 0 = all three functions are poor (physically vulnerable), 1 = all other.
Abbreviations: ADL, activities of daily living; CI, confidence interval; CRP, C-reactive protein; IADL, instrumental activities of daily living; IL-6, interleukin-6; MOS, medical outcome study; OR, odds ratio; TUG, Timed Up and Go.

55.0%), and III ($n = 37$, 23.1%) breast cancer. Of these, 66.9% were hormone receptor positive, 17.5% triple negative breast cancer, and 15.6% HER2 positive. Seventeen patients (10.6%) received neoadjuvant chemotherapy. The majority (65.6%) of the patients reported one or more comorbidities. Half of all participants were non-Hispanic white (50.3%) while the remainder were Hispanic (25.8%), black (10.7%), Asian (9.4%), and other (3.8%) (Table 1).

Physical Function Measures and Peripheral Blood Biomarkers Results

The distribution of the physical function measures and biomarkers are summarized in Table 2. The mean score of the Medical Outcomes Study (MOS) Physical Health (ADL) was 79.5 (SD, 22.6; range, 0–100). The mean IADL score was 12.3 (SD, 2.9; range, 4–14). The patient self-rated KPS ranged from 50–100 with over 85% of patients greater than 80. Physician-rated KPS ranged from 80–100 with over 95% of patients greater than 90. Thirty patients (21%) reported at least one fall in the last 6 months. The mean score on the TUG is 9.7 seconds (SD 2.2; range, 5–18).

The mean and median values of the three biomarkers were: IL-6, 3.4 and 1.9 pg/mL (SD 4.8, range undetectable–42.1); CRP, 5.5 and 2.8 μg/mL (SD 7.8, range 0.1–48.4); D-dimer, 0.8 and 0.6 μg/mL (SD 0.59, range 0.4–3.3) (Table 2). Interleukin-6 was modestly correlated with CRP ($r = .37$, $p < .001$). D-dimer was not correlated with IL-6 ($r = .12$, $p = .12$) or CRP ($r = .07$, $p = .35$).

The Association of Serum Biomarkers with Pre-Chemotherapy Physical Function Measurement

When treated as continuous variable, elevated D-dimer was associated with decreased ADL score of <70 ($p = .02$) and increased TUG score of ≥10 seconds ($p = .03$) (Table 3). There was no significant association between IL-6, CRP, and individual physical function measures when treated as continuous variable. There was no significant association between the biomarkers and patient self-rated- or physician-rated KPS. However, after combining the three objective measures of physical function (ADL, IADL, and TUG score), the poorest physical function group (defined by an ADL score of <70, IADL score of <14, and TUG score of >10 seconds) was associated with higher levels of IL-6 ($p = .05$), D-dimer ($p = .0004$), and CRP ($p = .05$). There were no significant changes in the association between the biomarkers of aging and physical function measures if the patients receiving neoadjuvant chemotherapy were excluded or included with the analysis (supplemental online Table 1).

The association of the biomarkers with patients' clinical characteristics (age, stage, hormone receptor status), type of chemotherapy (adjuvant vs. neoadjuvant chemotherapy), and number of comorbidities was evaluated (Table 4). A higher IL-6 level was associated with a higher breast cancer stage ($p < .001$). A higher D-dimer level was associated with older patient age ($p = .05$) and two or more comorbidities ($p < .001$). C-reactive protein was not associated with patient characteristics or type of chemotherapy and number of comorbidities. No association was observed between any of the three biomarkers and hormonal status.

After dichotomizing the biomarkers using the third quartile as a cutoff point, univariately, patients with higher IL-6 (≥5 pg/mL) and D-dimer (≥1 μg/mL) were 2 to 3 times more likely to have poorer physical function, indicated by each individual measure (ADL, IADL, and TUG) (Table 5). They were also 5 times more likely to be in the poorest physical function group using the combination of measures (OR 4.87, $p = .02$ for IL-6; OR

5.35, $p = .001$ for D-dimer). While there were no associations observed for CRP when looking at each function measure individually, patients with highest quartile of CRP ($\geq$6 μg/mL) were almost 4 times more likely to be in the poorest physical function group (OR 3.73, $p = .01$). Combining the three biomarkers and comparing those with patients with all three biomarkers in the lower three quartiles shows that those patients with at least two biomarkers in the fourth quartile were 18 times more likely to be in the poorest physical function group (OR 18.75, $p < .001$).

In multivariate analysis after adjusting for age, disease stage, number of comorbidities, and BMI, the associations between the individual biomarkers and physical function measures became non-significant. However, patients with IL-6 or CRP in the fourth quartile were over 3.5 (OR = 3.67, 95% CI, 1.10–12.23, $p = .03$) and 5.5 (OR = 5.75, 95% CI, 1.46–22.54, $p = .01$) times, respectively, more likely to be in the poorest physical function group (Table 6). The association between D-dimer and physical function was partially explained away by its association with age and comorbidity. Combining the three biomarkers and comparing those with patients with all three markers in the lower three quartiles showed that those with at least two biomarkers in the fourth quartile were over 14 times more likely to be in the poorest physical function group (OR 14.7, $p = .002$).

Discussion

This study adds to the oncology literature by demonstrating how biomarkers of aging are associated with poorer physical function among a cohort of patients with early stage breast cancer prior to receipt of chemotherapy. There is emerging literature demonstrating that markers of inflammation and coagulation are potential biomarkers of aging; however, few studies have evaluated their utility in patients with cancer. In addition, few studies have focused on the utility of these biomarkers across the aging spectrum. This study demonstrated that elevated pre-chemotherapy levels in at least two of the three peripheral biomarkers (IL-6, CRP, and D-dimer) are associated with poorest physical function as measured by the ADL scale, IADL scale, and TUG score. On the other hand, standard oncology performance status measures (KPS—either physician-rated or patient self-rated) were not associated with pre-chemotherapy IL-6, CRP, or D-dimer. There was limited variability in KPS values in this relatively healthy population (i.e., the majority of the patients had a KPS value of 90–100), and, hence, there was limited ability to statistically identify an association of KPS with biomarkers of aging.

There are several studies reported in the geriatric literature demonstrating an association between elevated markers of chronic inflammation (IL-6 and CRP) and coagulation factor (D-dimer) with physical functional decline and increased risk of mortality [6, 7, 9, 11, 13, 14]. In a cohort of 1,727 community-dwelling adults age 70 and older, elevated levels of IL-6 and D-dimer were associated with subsequent functional decline, cognitive decline, and mortality [15]. Interleukin-6 levels increased with patient age ($p = .0001$) even when controlling for comorbidities such as cancer, heart attack, hypertension, diabetes, or arthritis. In the same population, elevated D-dimer was predictive of cognitive decline over a 4-year period ($p < .01$) even after controlling for demographics, functional status, and comorbidity [13]. Furthermore, in another study of 4,735 community-dwelling adults age 65 and over, serum levels of CRP and D-dimer were associated with clinical frailty [11], defined by the criteria proposed by Fried et al. [16]. This association between increased plasma IL-6, CRP, and D-dimer levels and functional status suggests that deregulation of these inflammatory and coagulation factors may be related to the functional decline seen with aging, thus reflecting the overall health status of patients. Despite this understanding of the association of these biomarkers with aging, functional decline, and mortality, their utility in understanding the biologic age of patients with cancer has not been established.

In the field of oncology, these biomarkers have primarily been utilized to evaluate tumor-specific characteristics and risk (rather than host markers of aging and functional reserve). For example, among patients with metastatic breast cancer, elevated serum IL-6 is associated with poorer response to chemotherapy and shorter overall survival [17]. Elevated CRP levels at the time of diagnosis of breast cancer are associated with reduced overall and disease-free survival and with an increased risk of death from breast cancer [7]. Among patients with operable breast cancer, elevated plasma D-dimer levels were associated with lymphovascular invasion, higher clinical stage, and lymph node involvement [18].

There is a strong rationale for merging the fields of geriatrics and oncology by evaluating biomarkers of aging in patients with cancer. For example, breast cancer is a disease of aging, and almost half of all newly diagnosed cases are found in women aged 60 and older [2]. Adjuvant chemotherapy for early stage breast cancer decreases the risk of relapse and mortality from breast cancer [19–21]. However, chemotherapy comes with a risk for toxicity, functional decline, and treatment-related mortality [3–5]. Although older adults are at increased risk for toxicity, chronological age itself is a poor predictor of this risk, and, thus, there is a need to identify biomarkers that accurately reflect functional age. In a recent review of biomarkers and cancer and aging research, the authors proposed that the "ideal marker would reflect the degree of functional reserve and predict tolerance to cancer treatment" [22]. The current study demonstrates the association between combined biomarkers (IL-6, CRP, and D-dimer) with functional reserve (as measured by the MOS-Physical ADL scale, IADL scale, and TUG score). Subsequent analyses will evaluate the association of these biomarkers with chemotherapy toxicity.

There are limitations to this study. First, participation in the biomarker component was optional, and only 78% (160 out of 206) of patients participated. Second, typically, biomarkers of aging are studied among older adults; however, in this study we chose to include patients across the aging spectrum in order to include patients with a spectrum of physical function and risk of chemotherapy toxicity. Furthermore, these results need to be validated in an independent sample of patients. An ongoing multicenter study of patients with breast cancer ($n = 500$) evaluating the utility of these biomarkers of aging is under way (clinicaltrials.gov identifier NCT01472094). This study will also include two timepoints (baseline and post-chemotherapy) for collection of biomarkers of aging. Lastly, other potential biomarkers of aging, such as telomere length [23–26], $P16^{INK4a}$ [27], and sarcopenia [28], were not evaluated in this study but may contribute to determining the

degree of functional reserve in order to predict tolerance to cancer treatment.

Conclusion

Pre-chemotherapy biomarkers of aging are associated with poorer physical function among patients with breast cancer. This study furthers our understanding of the association of biomarkers of aging and pre-chemotherapy physical function in patients with early stage breast cancer prior to chemotherapy. It unites the fields of geriatrics and oncology by incorporating peripheral blood biomarkers of aging in patients across the aging spectrum. Studies are under way to evaluate the association between biomarkers of aging and chemotherapy toxicity. A multicenter R01 funded study is under way to confirm these results (clinicaltrials.gov identifier NCT01472094).

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Author Contributions

Conception/design: Arti Hurria, Yuan Yuan

Provision of study material or patients: Arti Hurria, Yuan Yuan, Daneng Li, Joanne Mortimer, Thehang Luu, George Somlo, James Waisman, Joseph Chao, Shu Mi

Collection and/or assembly of data: Laura Zavala, Susan E. Yost, Arti Hurria, Jennifer Choi, Nilesh Vora, Yuan Yuan, Canlan Sun, David Smith, Daneng Li, Joanne Mortimer, Thehang Luu, George Somlo, James Waisman, Joseph Chao, Vani Katheria, Timothy W. Synold, Vivi Tran, Shu Mi, Tao Feng, Abrahm Levi, Anait Arsenyan

Data analysis and interpretation: Laura Zavala, Susan E. Yost, Arti Hurria, Jennifer Choi, Nilesh Vora, Yuan Yuan, Canlan Sun, David Smith, Daneng Li, Joanne Mortimer, Thehang Luu, George Somlo, James Waisman, Joseph Chao, Vani Katheria, Timothy W. Synold, Vivi Tran, Shu Mi, Tao Feng, Abrahm Levi, Anait Arsenyan

Manuscript writing: Susan E. Yost, Arti Hurria, Yuan Yuan

Final approval of manuscript: Laura Zavala, Susan E. Yost, Arti Hurria, Jennifer Choi, Nilesh Vora, Yuan Yuan, Canlan Sun, David Smith, Daneng Li, Joanne Mortimer, Thehang Luu, George Somlo, James Waisman, Joseph Chao, Vani Katheria, Timothy W. Synold, Vivi Tran, Shu Mi, Tao Feng, Abrahm Levi, Anait Arsenyan

Disclosures

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For Further Reading:

Marloes G.M. Derks, Nienke A. de Glas, Esther Bastiaannet et al. Physical Functioning in Older Patients With Breast Cancer: A Prospective Cohort Study in the TEAM Trial. ***The Oncologist*** 2016;21:946-953.

Implications for Practice:

Although older patients constitute a large share of the breast cancer population, little is known about the effect and consequences of treatment of breast cancer in this specific age group. This study revealed that, unlike younger patients, older patients do not regain their physical abilities after surgical and adjuvant treatment for breast cancer. In older adults, the effect of treatment on physical functioning and independency could be more relevant than survival outcomes. Clinicians and older patients should be aware of the impact of treatment on physical functioning and prevent older patients from experiencing physical decline, which could lead to institutionalization and loss of independence. There is a need for age-specific guidelines that take into account the heterogeneity of the older population and for evidence-based treatment that focuses not only on cancer-specific outcomes but also on the consequences of treatment for physical and cognitive functioning and quality of life.