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Frailty and Long-term Mortality Of Older Breast Cancer Patients: CALGB 369901 (Alliance)

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Abstract

Purpose—Breast cancer patients aged 65+ (“older”) vary in frailty status. We tested whether a deficits accumulation frailty index predicted long-term mortality.

Methods—Older patients (n=1280) with non-metastatic, invasive breast cancer were recruited from 78 Alliance sites from 2004-2011, with follow-up to 2015. Frailty categories (robust, pre-frail, and frail) were based on 35 baseline illness and function items. Cox proportional hazards and competing risk models were used to calculate all-cause and breast cancer-specific mortality for up to 7-years, respectively. Potential covariates included demographic, psychosocial, and clinical factors, diagnosis year, and care setting.

Results—Patients were 65-91 years old. Most (76.6%) were robust; 18.3% were pre-frail, and 5.1% frail. Robust patients tended to receive more chemotherapy +/- hormonal therapy (vs. hormonal) than pre-frail or frail patients (45% vs. 37% and 36%, p=.06), and had the highest adherence to hormonal therapy. The adjusted hazard ratios for all-cause mortality (n=209 deaths) were 1.7 (95% CI 1.2-2.4) and 2.4 (95% CI 1.5-4.0) for pre-frail and frail vs. robust women, respectively, with an absolute mortality difference of 23.5%. The adjusted hazard of breast cancer death (n=99) was 3.1 (95% CI 1.6-5.8) times higher for frail vs. robust patients (absolute difference of 14%). Treatment differences didn't account for the relationships between frailty and mortality.

Conclusions—Most older breast cancer patients are robust and could consider chemotherapy where otherwise indicated. Patients who are frail or pre-frail have elevated long-term all-cause and breast-cancer mortality. Frailty indices could be useful for treatment decision-making and care planning with older patients.

Keywords

older; breast cancer; frailty; survival; mortality

Introduction

The absolute number of breast cancer patients aged 65 and older (“older”) is projected to increase rapidly over the coming decades.¹ These older patients exhibit variability in health and system reserve, even at similar chronological ages.²⁻⁴ Clinically meaningful decrements in reserve are not always apparent and can go unrecognized in routine oncology encounters.⁵ Knowledge about system reserve could influence treatment decision-making,^{3,6} and predict tolerance of systemic therapy and survival.⁷⁻⁹

Frailty is a construct that captures system reserve and ability to withstand stressors like cancer and its therapies.^{7,10-12} Frailty is generally measured using one of two types of indices -- phenotypic, using a comprehensive clinical geriatric assessment focused on observed manifestations of system reserve failure (e.g., loss of muscle strength, fatigue),^{10,11} and deficits accumulation based on illnesses and ability to function to perform daily activities.¹³⁻¹⁶

Deficits accumulation frailty indices utilize readily available clinical data and easily obtained patient-reported information and have been found to reliably predict hospitalization and mortality of community-dwelling older individuals.^{12,17-19} However, they are not frequently used in older cancer populations,²⁰ despite greater ease of use than comprehensive clinical geriatric assessments. When deficits accumulation indices have been applied in oncology settings, they have predicted initiation of hormonal therapy in older breast cancer patients,²¹ chemotherapy toxicity,⁷ accelerated cancer-related cognitive decline,²² and two-year all-cause mortality.²⁰ However, there are no modern data on the ability of deficits accumulation indices to predict long-term breast cancer outcomes.

In this study we used data from a well-characterized cohort of breast cancer patients followed prospectively for up to seven years to determine if a deficits accumulation frailty index predicted all-cause and breast cancer-specific mortality. The results are intended to inform development of online or electronic medical record based systems to assist in frailty assessment, and facilitate treatment decision-making and care planning with older patients.^{7,23} The ease of administration and predictive validity of deficits accumulation indices could provide a novel approach to expand the reach of frailty measurement in routine oncology practice settings.

Methods

The study (CALGB 369901) was conducted at 78 Cancer and Leukemia Group B (CALGB) sites, now part of the Alliance for Clinical Trials in Oncology. The study has been described elsewhere.^{22,24} Briefly, breast cancer patients signed an IRB-approved consent to participate in a study evaluating preferences for systemic therapy and effects of treatment on quality of life and survival. Follow-up data were used to conduct a planned secondary analysis of mortality as a function of frailty.

Setting and Population

Patients were diagnosed between January 1, 2004 and April 1, 2011 with follow-up to April 1, 2015. Prior reports included earlier subsets of patients and/or shorter-term follow-up.^{21,25-27} Eligible patients were 65 years or older, were diagnosed with primary invasive non-metastatic breast cancer, spoke English or Spanish, passed an entry cognitive screen using the Blessed Orientation, Memory and Concentration test,²⁸ and were within 20 weeks of definitive surgery.

Data Collection

Site clinical research associates confirmed eligibility, obtained permission to contact patients (received for 95%), obtained consent, abstracted records, and determined distant recurrences

and vital status annually for up to 7-years. The Alliance Statistics and Data Center managed registration and clinical data collection. Interviews were conducted from a centralized site using a computer-assisted, interviewer-administered, structured instrument.²⁴

Outcome Variables

The primary outcomes were all-cause and breast cancer-specific mortality. Vital status records from the sites were compared with data from the National Death Index²⁹ from January 1, 2004 to December 31, 2014 to verify date and cause of death. Per protocol matching to the National Death Index was based on birthdate, name, race, gender, social security number (if available), marital status, and state. Patients with records in the National Death Index database were considered deceased. Those without records in the National Death Index were considered alive on December 31, 2014, or the date last known alive, whichever came last. Vital status was concordant for site and National Death Index records for 96% of patients. If results were discordant (4%) or unknown (<1%), the patient was considered deceased if either source noted death.

Patients were defined as dying of breast cancer if noted in either source or there was an indication of death from metastases to the brain, lung, liver, and/or bone. Patients that died of breast cancer were confirmed as having distant recurrences; two patients died of treatment toxicity within the first year without recurrence and their deaths were attributed to breast cancer. Patients were coded as having non-breast cancer death if the cause was not related to breast cancer, was uncertain (e.g., cardiac arrest, septicemia, or pneumonia), or there was death from a non-breast cancer cause after a recurrence (n=8). Death dates were concordant in almost all cases; if dates varied, the National Death Index date was used.

Independent Variables

The primary independent variable was patient-reported frailty at baseline. The Searle deficits accumulation frailty index, developed to predict mortality in general older populations, was adapted to the cancer setting.^{12,19} The adaptation for breast cancer patients has been shown to predict hormonal therapy initiation²¹ and trajectories of cognitive function.²²

The 35-item index is summarized in eTable 1, and includes comorbidities in the year prior to diagnosis; self-report of pre-diagnosis physical, social, role, and emotional function³⁰; and pre-diagnosis activities of daily living (ADLs) and instrumental activities of daily living (IADLs).³¹ Each item is scored from 0-1, with 1 indicating greater frailty. Scores were summed, averaged across the number of non-missing items, and standardized to yield a score between zero and one, where a higher score indicated greater frailty. We required that data were available for 31 of 35 items for scoring (e.g., <10% missing). Scores were categorized based on established cut-points related to mortality: robust= 0 to < 0.2; pre-frail= 0.2 to < 0.35; and frail 0.35 to 1.^{7,12,19,32-34}

Covariates

Several baseline factors were considered as covariates based on known relationships with frailty and/or mortality, including age, race (white vs. non-white), education (high school vs. > high school), marital status (married at enrollment vs. other), home ownership as a

proxy for household wealth (yes/no), tangible and emotional social support from the Medical Outcomes Study,³⁵ optimism (as a personality factor linked to survival),³⁶ and year of diagnosis (2005, 2006-2008, and 2009+). We also considered American Joint Committee on Cancer (AJCC)-6 summary stage, surgery (mastectomy vs. lumpectomy), estrogen (ER)-receptor status, composite systemic treatment initiated at diagnosis (chemotherapy +/- hormonal therapy vs. hormonal only), months known to be adherent to hormonal therapy (among ER+ cases who initiated treatment, and type of enrolling site (community affiliate vs. academic). Data were not collected on radiation use.

Statistical Analysis—Mortality was determined from diagnosis to the last known contact or 7-years, whichever came last. All-cause mortality rates were estimated using the complement of Kaplan-Meier estimates; the log-rank test was used to test if unadjusted mortality rates differed by frailty category. After verifying proportionality assumptions, univariable Cox proportional hazards models were used to evaluate the impact of covariates on all-cause mortality. Multivariable Cox models were used to test the independent effects of frailty, considering covariates. Variables were considered for inclusion in the multivariable model based on having a relationship with mortality in univariable Cox analyses ($p \leq 0.10$). Backward elimination was used to determine the final model. Variables significant at $p \leq 0.10$ were retained in the final model. Model performance was assessed using Harrell's C-index.³⁷

Breast cancer-specific mortality rates were estimated by frailty category using cumulative incidence functions; Gray's tests were used to assess whether rates differed by frailty category. Competing risk models were then used to estimate the impact of frailty on breast cancer (vs. non-breast cancer) mortality, adjusting for covariates. Covariate selection was based on backward elimination until deletion of any variables did not improve model fit based on the BICcr criterion.³⁸ Recurrence was not included in the models since all patients who died of breast cancer had recurrences (except for two dying of chemotherapy toxicity).

Finally, separate exploratory analyses were conducted among ER+ patients to test if adherence to hormonal therapy affected the frailty-mortality relationships by determining the hazards for frailty in final models with and without adherence. All analyses were done using R statistical software, version 3.1.2³⁹ on a database locked on April 1, 2015.

Results

There were 1528 eligible patients; 83.7% ($n=1280$) completed baseline interviews and constitute the final cohort (Figure 1). The interviewed vs. non-interviewed patients had slightly lower all-cause (18% vs. 29%) and breast cancer (9% vs. 11%) mortality rates by 7-years.

The cohort ranged from 65 to 91 years old (mean 72.4, SD 5.9 (Table 1). Most (88%) were White, 42% had high school or less education, and 55% were married at enrollment. Among the 1265 patients with frailty data (98.8% of the cohort), the majority (76.6%) scored in the robust category, 18.3% were pre-frail, and only 5.1% were frail (eFigure 1).

Patients in the frail and pre-frail groups were older than the robust group, but there were no differences in race, education, or cancer clinical characteristics by frailty category (Table 2).

There was a trend for those who were robust to have more chemotherapy (+/- hormonal therapy) than those who were pre-frail or frail (45% vs. 37% and 36%, $p=.06$), but there were no differences in the types of chemotherapy by frailty group. There were a total of 209 deaths among those with frailty data: 53% due to non-breast cancer causes and 47% due to breast cancer.

All-cause Mortality

There were significant differences in all-cause mortality rates by frailty category, with an absolute difference of 23.5% between the robust and frail groups at seven years (Figure 2). Moreover, the frail group had a steeper slope of mortality than the other groups after the first year. Several socio-demographic and psychosocial variables were also related to all-cause mortality in univariable analyses, including older age, not being a homeowner, reporting less optimism, being unmarried, and having less emotional support (Table 1). Since about one-half of all deaths were breast cancer deaths, clinical prognostic factors, such as stage and ER-status, were also associated with all-cause mortality, but systemic treatment was not statistically significantly associated with mortality. There were no effects of enrollment year on mortality.

After considering covariates, only age, frailty, and cancer-related clinical factors were associated with mortality rates, and systemic treatment remained non-significant (Table 3). The hazards of all-cause mortality increased in a dose-response manner with increasing frailty category, with hazards ratios that were 1.7 (95% CI 1.2-2.4) and 2.4 (95% CI 1.5-4.0) times higher for pre-frail and frail vs. robust women, respectively.

Breast-cancer Specific Mortality

Frailty demonstrated a dose-response relationship with breast cancer mortality after considering age, stage, and ER status. The magnitude of the hazard ratio for frail (vs. robust) (HR 3.1 [95% CI 1.6-5.8]) was similar to that of having node positive cancer (i.e., stage 2b or greater vs. stage 1) (HR 3.5 [95% CI 2.1-6.0]) (Table 3). Having ER-negative cancer, but not surgery type or systemic treatment, was associated with breast cancer mortality, after considering covariates.

Finally, among ER+ patients, greater adherence to hormonal therapy reduced the hazard of all-cause and breast cancer death, but the frailty hazards ratios for each mortality outcome remained unchanged with adherence in the model (not shown).

Discussion

This is the first study to use a deficits accumulation index to examine frailty and long-term mortality outcomes in a large cohort of older non-metastatic breast cancer patients. The results indicate, as expected, that frailty is a strong predictor of all-cause and breast cancer-specific mortality up to 7-years post-diagnosis. Patients who were frail showed accelerated mortality rates as early as one year after diagnosis, and those who were pre-frail had parallel, but higher death rates than those who were robust. However, most patients were robust and the overall mortality rates were low, with similar rates of breast cancer as non-breast cancer deaths.

The finding that a deficits accumulation frailty index predicts mortality in an older breast cancer population supports the potential value of integrating frailty assessment into diagnostic evaluations and treatment decisions. Current widely used treatment decision tools like *Adjuvant! Online*⁴⁰ or PREDICT⁴¹ consider comorbidity, but do not include frailty.^{42,43} Tools such as Eastern Cooperative Oncology Group (ECOG) performance status are poor predictors of mortality in older patients.⁴⁴ Other indices such as e-prognosis include some aspects of deficits accumulation, but were developed for general populations¹⁷ but an under-estimate short-term survival of breast cancer patients²⁰ who have better non-cancer survival than age-matched peers without cancer.⁴⁵⁻⁴⁷ Other frailty tools that combine deficits accumulation and phenotypic measures have been developed in younger breast cancer populations,⁴⁸ and for patients with multiple types of cancer,^{7,49,50} with varying results across cancer types,^{50,51} suggesting that disease-specific tools may be needed.

The deficits accumulation frailty index used in this study used data on comorbidity and functional status to capture system reserve and physiological, rather than chronological age.^{4,7} The functional status items were derived from two short, easy to administer patient-report scales. Since comorbidity is routinely collected, addition of short, questionnaire-based functional assessments could provide a feasible frailty assessment for use in clinical encounters and inclusion in electronic health records, thereby increasing the reach of geriatric assessment in practice settings. Functional data could either be reported by patients prior to the visit, ascertained by nursing staff, or asked by physicians during encounters. Prior research has noted that a limited number of self-reported functional status questions significantly predict 10-year all-cause survival in older non-metastatic breast cancer patients, although those data were not combined with comorbidity or other data in a frailty index or to predict breast cancer-specific mortality.^{52,53} Prior to recommendations about implementation, it will be important to assess the most efficient method to collect data in routine practice. It will also be necessary to compare the predictive ability of the deficits accumulation frailty index used in this study to phenotypic frailty index approaches, and to demonstrate in randomized trials that routine use of frailty measures improves patient satisfaction and cancer-related outcomes.

There were very few older patients in this cohort with scores in the frail range (5.1%). This group is generally clinically apparent, but recognition of this subset is important since they had more steeply rising death rates than the other groups starting one year after diagnosis, suggestive of a group with accelerating aging.^{2,22} This group is very likely to experience treatment toxicity⁹ and to require monitoring and assistance during survivorship care. The pre-frail group constituted almost one-fifth of the cohort, and also had significantly higher mortality rates than robust patients, but their death rates increased over time in parallel with the robust group, suggesting a phase shift.^{2,22} The pre-frail group can be less readily apparent in clinical encounters⁵ and clinicians generally do not accurately estimate their life expectancy.⁴⁷ Thus, the results of this analysis suggest that this index or other tools could have utility in clinical treatment decision-making and surveillance during survivorship care by distinguishing those who are pre-frail from those who are robust.

This cohort of older patients had low overall death rates (less than 17% all-cause or breast cancer death up to seven-years). There were also an equal number of breast cancer and non-

breast cancer deaths. This result suggests that for the overwhelming majority who are robust, treatment decision-making should target reduction in the risk of breast cancer death, and not assume that robust older patients are more likely to die of other causes rather than breast cancer. Additionally, there were no differences in the cancer clinical characteristics of the frail and pre-frail patients compared to robust patients, and despite a trend for less chemotherapy use (+/- hormonal therapy) in the frail vs. robust patients, the relationship between frailty and breast cancer mortality was not due to measured chemotherapy or hormonal treatment adherence differences. However, there could have been unmeasured chemotherapy dose-reductions, or changes in types of hormonal therapy employed over time. Another explanation for the relationship between frailty and breast cancer mortality is that certain comorbidities like diabetes contribute separately to frailty and breast cancer biology. Alternatively, biomarkers of frailty such as elevated cytokine levels (e.g., IL6) might be associated with poor breast cancer prognosis, perhaps via up-regulation of angiogenesis.^{54,55} Future research will be required to elucidate the direct effects of aging-related processes and diseases on breast cancer prognosis.

While this study has several strengths including the long-term follow-up of a large and well-defined older cohort and use of an established deficits accumulation frailty index, some limitations should be considered in evaluating the results. First, although the index used in this study was multi-dimensional, it did not include phenotypic frailty data such as falls, organ reserve (e.g., renal function, hemoglobin, or liver function), and biomechanical measures of function and muscle mass (e.g., VO₂ max, grip strength). These two approaches to frailty measurement should be compared for accuracy and effort in data collection.⁵⁰ Next, the frailty index relied on self-report for the period prior to diagnosis. Since self-report is fairly accurate⁵⁶ or over-estimates function, self-report is likely to bias results for the association between the deficits accumulation frailty index and death toward the null. We used baseline enrollment frailty for its relevance to treatment decision-making. If robust or pre-frail patients became frail over time, or frail patients returned to a robust category, this should have biased results for the association of frailty and mortality toward the null.

Another limitation is that this cohort may not be representative since they had a higher proportion of robust patients than seen in non-cancer settings.⁵⁷⁻⁵⁹ This is likely to reflect the observation that breast cancer patients are healthier than their non-cancer peers.⁴⁵ Despite most patients being recruited from community settings, the cohort is also likely to be more robust than general older breast cancer populations due to volunteer biases. This should under-estimate population mortality rates and biased our results for the association between frailty and mortality towards the null, suggesting that the index might have higher predictive potential in general breast cancer populations. Finally, we did not have data on dose reductions, the percent of cycles completed, radiation, HER2 status and trastuzumab use, or changes in hormonal regimens over time. These data will be important to confirm the lack of clinically meaningful effect of treatment regimens on the frailty-mortality relationship.

This study describes long-term mortality of older breast cancer patients and provides important evidence to support the need for tailoring care based on physiological rather than chronological age.³ The results suggest that most older breast cancer patients are robust and

could consider chemotherapy if otherwise indicated, and that frailer patients might continue to benefit from adherence to hormonal therapy. Overall, deficits accumulation indices could be a useful and practical method to assess frailty in routine practice and inform treatment decision-making and survivorship care planning with older patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Study Sample of Older Patients with Newly Diagnosed, Non-Metastatic Breast Cancer Followed for Vital Status for up to 7 years

Legend for Figure 1. The figure provides the study schema for enrollment and analysis.

Note: compared to an earlier report from this cohort that included 1529 eligible and 1288 patients²¹, one participant was found later to be ineligible and 8 women subsequently withdrew consent. The final cohort in the locked dataset included 1280 patients. Among the 15 patients with missing frailty data (1.2%), 12 were alive at last known follow-up and 3 died of breast cancer.

Baseline Characteristics of Older Breast Cancer Patients and Unadjusted Associations with Mortality[†] for up to Seven Years of Follow-up**Table 1**

Characteristic	Total N=1280 ² N (%) or mean (SD)	All-cause Death HR (95% CI)	P-value	Breast cancer-specific death HR (95% CI)	P-value
Number of deaths	212	110		112	
Socio-demographics					
Age, per 1-year increase	Mean (SD)	1.1 (1.1-1.1)	0.001	1.0 (1.0-1.1)	0.001
Race	Non-white	1		1	
	White	1.3 (0.8-2.0)	0.30	1.0 (0.6-1.9)	0.92
Education	HS	1		1	
	>HS	0.9 (0.7-1.1)	0.26	0.9 (0.6-1.3)	0.47
Home ownership	No	1			
	Yes	1.6 (1.1-2.2)	0.009	1.7 (1.1-2.8)	0.03
Marital Status	Married	1		1	
	Not married	1.5 (1.2-2.0)	0.003	1.3 (0.9-1.9)	0.21
Frailty					
	Robust	1		1	
	Pre-frail	1.9 (1.4-2.6)	0.001	1.8 (1.2-2.9)	0.009
	Frail	3.2 (2.0-5.0)	0.001	3.4 (1.8-6.3)	<0.001
Psychosocial³					
Emotional support, per 1-point increase	Mean (SD)	0.8 (0.7-1.0)	0.03	0.9 (0.7-1.2)	0.43
Tangible support, per 1-point increase	Mean (SD)	0.9 (0.8-1.0)	0.22	0.9 (0.8-1.2)	0.54
Optimism, per 1-point increase	Mean (SD)	0.8 (0.7-1)	0.02	0.9 (0.7-1.1)	0.27
Clinical Breast Cancer Characteristics					
AJCC 6 Stage	Stage 1	1		1	
	Stage 2a	1.3 (0.9-1.8)	0.11	1.7 (1.0-3.0)	0.041
	2b+	2.0 (1.4-2.7)	0.001	4.2 (2.6-6.7)	<0.001
Recurrence	No	1		1	
	Yes	6.3 (4.8-8.4)	0.001	19.9 (13.3-29.7)	<0.001
Surgery	BCS	1		1	

Characteristic	Total N=1280 ² N (%) or mean (SD)	All-cause Death HR (95% CI)	P-value	Breast cancer-specific death HR (95% CI)	P-value
Number of deaths	212	110		112	
ER Status	Mastectomy	1.6 (1.2-2.1)	0.001	2.1 (1.4-3.1)	<0.001
	Negative	216 (17%)		1	
	Positive	1062 (83%)	0.01	0.4 (0.2-0.6)	<0.001
Composite Systemic Rx	Chemo (+/- HT)	519 (43%)		1	
	HT only	687(57%)	0.30	0.5 (0.3-0.7)	<0.001
Adherence to hormonal therapy among ER+ ⁴					
Mean (SD), months	33.1(23.0)	0.99(0.98-0.99)	<0.001	0.98(0.97-0.99)	<0.001
Year of Diagnosis (and enrollment)					
2005	307 (24%)	1		1	
2006-2008	644 (50%)	0.8 (0.6-1.2)	0.30	0.9 (0.6-1.5)	0.80
2009+	329 (26%)	0.9 (0. 6-1.3)	0.45	0.9 (0.5-1.6)	0.62
Site of Enrollment					
Main academic site	366 (29%)	1			
Community affiliate	914 (71%)	0.8(0.6-1.1)	0.27	1.1 (0.7-1.7)	0.64

¹ Associations of covariates and all-cause and breast cancer-specific mortality outcomes and covariates were assessed using univariable Cox proportional hazards and competing risk models, respectively. Hazards of 1 represent the referent group. Note that there were 15 who were missing frailty data and of these patients, 12 were alive and 3 had died of breast cancer at the last follow-up.

² Numbers may not total 1280 due to missing data for some variables.

³ Scores on the emotional and tangible support range from 1-5; optimism scores range from 1-5.

⁴ Hormonal adherence data are presented for the ER-positive patients. Among the 1062 ER-positive patients, 1017 initiated therapy (96%); of these 990 (97.3) had data on adherence that was used to calculate the mean number of months of treatment adherence.

AJCC-6= American Joint Committee on Cancer v.6

Chemo = chemotherapy

HT = hormonal therapy

HS=high school

Table 2
Clinical Characteristics of Older Breast Cancer Patients by Frailty Group[†]

Variables	Total N=1265	Robust n=970 (76.7%)	Pre-frail N=231 (18.3%)	Frail N=64 (5.1%)	P-value
Age, Mean(SD)	72.4 (5.9)	71.8 (5.7)	73.7 (6.4)	75.1 (6.9)	<.001
Comorbidity					
2 illnesses	561 (44%)	526 (54%)	33 (14%)	2 (3%)	<.001
>2 illnesses	704 (56%)	444 (46%)	198 (86%)	62 (97%)	
Race					
Non-White	151 (12%)	112 (12%)	31 (13%)	8 (12%)	0.69
White	1114 (88%)	858 (88%)	200 (87%)	56 (88%)	
Education					
High school or less	532 (42%)	395 (41%)	107 (47%)	30 (47%)	0.20
> High school	732 (58%)	575 (59%)	123 (53%)	34 (53%)	
Marital Status					
Married	701 (55%)	563 (58%)	110 (48%)	28 (44%)	0.003
Not married	564 (45%)	407 (42%)	121 (52%)	36 (56%)	
Year of diagnosis					
<=2005	307 (24%)	231 (24%)	57 (25%)	19 (30%)	0.71
2006-2008	642 (51%)	498 (51%)	117 (51%)	27 (42%)	
2009+	316 (25%)	241 (25%)	57 (25%)	18 (28%)	
AJCC-6 Stage					
I	579 (46%)	453 (47%)	99 (43%)	27 (42)	0.39
2a	397 (31%)	305 (31%)	75 (32%)	17 (27%)	
2b or 3	289 (23%)	212 (22%)	57 (25%)	20 (31%)	
Surgery					
BCS	857 (68%)	660 (68%)	159 (69%)	38 (60%)	0.42
Mastectomy	407 (32%)	310 (32%)	72 (31%)	25 (40%)	
ER status					
Negative	212 (17%)	167 (17%)	33 (14%)	12 (19%)	0.54

Variables	Total N=1265	Robust n=970 (76.7%)	Pre-frail N=231 (18.3%)	Frail N=64 (5.1%)	P-value
Positive	1051 (83%)	803 (83%)	196 (86%)	52 (81%)	
Composite systemic treatment					
Chemotherapy +/- hormonal	510 (40%)	410 (45%)	79 (37%)	21 (36%)	0.06
Hormonal only	682 (54%)	509 (55%)	135 (63%)	38 (64%)	
Type of chemotherapy					
AC based	309 (61%)	251(61%)	44 (56%)	14 (67%)	0.54
Other	200 (39%)	158 (39%)	35 (44%)	7 (33%)	
Hormonal therapy initiation (among ER positive) ²					
Yes	1007 (96%)	774 (96%)	185 (94%)	48 (92%)	0.15
No	44 (4%)	29 (4%)	11 (6%)	4 (8%)	
Adherence to hormonal therapy (among initiators) ²					
Mean (SD), months	33.1 (23.0)	34.4 (23.1)	29.0 (22.4)	26.7 (22.3)	0.003
Recurrence					
No	1138 (90%)	879 (91%)	207 (90%)	52 (81%)	--
Yes	125 (10%)	90 (9%)	23 (10%)	12 (19%)	

¹There were 1280 women in the cohort; frailty scores were missing for 15 due to missing items on the 35-item scale, so the data on the table and in subsequent analyses are based on 1265 women with frailty data.

²Hormonal adherence data are presented for the ER-positive patients. Among the 1062 ER-positive patients, 1017 initiated therapy (96%); of these 990 (97.3) had data on adherence that was used to calculate the mean number of months of treatment adherence.

Some numbers may not total to 1265 (100%) due to missing data for individual variables.

AJCC-6= American Joint Committee on Cancer v.6

Table 3
Adjusted Hazards Ratios for Associations with Mortality Outcomes by Frailty Category
Among Older Patients with Non-metastatic Breast Cancer Followed for up to Seven Years

	All-cause Mortality ¹		Breast Cancer-Specific Mortality ²	
Covariate	HR (95% CI)	P value	HR (95% CI)	P value
Frailty				
Robust	1.0 (referent)		1 (referent)	
Pre-frail	1.7 (1.2-2.4)	.002	1.6 (1.0-2.6)	.060
Frail	2.4 (1.5-4.0)	.0003	3.1 (1.6-5.8)	.001
Age (per 1 year increase)	1.1 (1.1-1.2)	< .0001	1.1 (1.01-1.1)	.005
Stage				
1	1 (referent)		1 (referent)	
2a	1.3 (0.9-1.8)	.200	1.6 (0.9-2.7)	.100
2b+	1.7 (1.2-2.5)	.003	3.5 (2.1-6.0)	<.0001
Estrogen receptor				
Negative	1 (referent)		1 (referent)	
Positive	0.7 (0.5-0.9)	.020	0.4 (0.2-0.6)	<.0001
Surgery				
BCS	1 (referent)		-----	
MST	1.3 (1.0-1.8)	.099		
Harrell's C	0.69		N/A	

¹ Cox-proportional hazards model for 1265 participants with frailty data

² Competing risk model for 1265 participants with frailty data

Note: Treatment is not statistically significantly related to mortality after controlling for stage and ER status, so it is not retained in the final models.