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Original Article

The impact of frailty on breast cancer outcomes: evidence from analysis of the Nationwide Inpatient Sample, 2005-2018

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Abstract: The aims of the present study were to examine whether and how frailty impacts the outcomes of breast cancer. Data of women with breast cancer hospitalized during 2005 and 2018 were extracted from the US Nationwide Inpatient Sample (NIS) database. Frailty was identified using a novel algorithm, Hospital Frailty Risk Score (HFRS). Propensity-score (PS) matching was utilized to balance the baseline characteristics between frail and non-frail groups. In-hospital mortality, unfavorable discharge, prolonged length of stay (LOS), and total hospital cost were compared using univariate and multivariable logistic regression analyses. A total of 19,522 patients with metastatic (frailty n = 9,906; no frailty n = 9,716) and 135,200 with non-metastatic breast cancer (frailty n = 30,235; no frailty n = 104,965) were included. After adjustment, frailty was significantly and independently associated with higher risk for in-hospital mortality, unfavorable discharge, prolonged LOS, and greater hospital cost in both metastatic and non-metastatic diseases, in which the impacts of frailty was greater in women with non-metastatic disease. In stratified analysis, frailty had the greatest impact on in-hospital mortality among women had had non-metastatic disease and aged <50 years (aOR = 3.88; 95% CI: 1.95-7.73). In conclusion, frailty is associated with worse outcomes in women with breast cancer, and the effects are greater in non-metastatic disease and younger patients.

Keywords: Frailty, hospital frailty risk score (HFRS), breast cancer, mortality, Nationwide Inpatient Sample (NIS)

Introduction

Breast cancer is the most frequent malignancy in women worldwide, and is curable in 70% to 80% of patients with early-stage, non-metastatic disease [1-3]. Advanced breast cancer with metastases to distant organs (stage IV disease), however, is considered incurable with currently available treatments [1-3]. Notably, besides lung cancer, breast cancer accounts for more cancer deaths in women than any malignancy in the United States [3]. A variety of modifiable and non-modifiable risk factors for breast cancer have been established by epidemiologic studies [3]. Non-modifiable factors include race, ethnicity, family history of cancer, and genetic traits, whereas modifiable factors include heavy alcohol consumption, physical inactivity, exogenous hormones, and certain female reproductive factors [3].

Frailty is considered a vulnerability to stress that increases the risk of adverse health outcomes and which is thought to be multifactorial [4-6]. Frailty has been defined as "a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure" [7]. While frailty is generally associated with advanced age, any person with advanced diseases or chronic health conditions can develop frailty [6]. A number of instruments are available to diagnose and categorize frailty, for instance, a widely used frailty criteria proposed by Fried et al. include: weakness, slow walking speed, low physical activity, self-reported exhaustion, and unintentional weight loss [8]. Diagnosis of frailty in individuals with an advanced disease requires the awareness of "biological age" instead of chronological age alone [4, 6].

Frailty has been studied in the field of oncology, and been found as a critical predictor of mortality and treatment toxicity in a number of malignancies, including: lung cancer, gastric cancer, urological cancer, and gynecological cancers [9-14]. A systematic review and meta-analysis by Dai et al. [12] evaluated the impact of frailty on the prognosis of lung cancer. The authors reported that compared to non-frail patients, frail patients had a 1.5 fold risk for death due to any cause and 2.6 fold risk for having therapeutic toxicity.

However, there have been few studies examining the role of frailty in patients with breast cancer, and most of them focused on its influence on quality of life (QoL) [15-18]. Yan et al. [19] studied the association between frailty and cancer-specific mortality in older women with breast cancer and found the degree of frailty was not associated with breast cancer-specific mortality; however, frail women had a significantly higher risk of all-cause mortality compared to robust women (HR = 2.32). Nevertheless, whether and how frailty poses greater risk on in-hospital outcomes such as length of stay (LOS), hospital cost or discharge destination in hospitalized women with breast cancer still needs to be determined. In addition, the previous studies did not separately analyze women with and without metastasis.

Given the emotional, financial, and healthcare burden breast cancer places on patients and society, an assessment of how frailty affects the outcomes of women admitted to hospitals with breast cancer is of special importance. Thus, the purpose of this study was to use a large cohort from the nationally representative database of the US to examine how frailty impacts outcomes in breast cancer patients.

Methods

Study design and data source

This was a population-based, retrospective study, using data extracted from the United States (US) Nationwide Inpatient Sample (NIS) database. The NIS is the largest all-payer, continuous inpatient care database, in the United States and includes data of about 8 million hospital stays each year [20]. The database is administered by the Healthcare Cost and Utilization Project (HCUP) of the US National Institutes of Health (NIH) [20]. Patient data include primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographic information, expected payment source, duration of hospital stay, and hospital characteristics (i.e., bed size/location/teaching status/hospital region). The NIS database is updated annually, and derives patient data from about 1,050 hospitals from 44 States in the US, and represents a 20% stratified sample of US community hospitals as defined by the American Hospital Association.

Ethics statement

All data were obtained through request to the Online Healthcare Cost and Utilization Project (HCUP) Central Distributor (available at: https://www.distributor.hcup-us.ahrq.gov/). This study conforms to the NIS data-use agreement with HCUP. Because this study analyzed secondary data from the NIS database, patients and the public were not involved directly. The study protocol was submitted to the Institutional Review Board (IRB) of Tri-Services General Hospital, which exempted the study from IRB approval. Since all data in the NIS database were de-identified, the requirement for informed consent was also waived.

Study population

Inclusion criteria was women hospitalized between 2005 and 2018 aged 40 years or older who had a primary discharge diagnosis of breast cancer, identified in the NIS database using International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes: 174.0-174.9, V10.3, C50.x11, C50.x12, C50.x19, Z85.3. Exclusion criteria were breast cancer *in situ* (233.0 or D05), cancer metastatic to the breast (198.81 or C79.81), and breast cancer of uncertain behavior/unspecific nature (238.3, 239.3, D48.6, or D49.3). Individuals without complete in-patient data were excluded. Since metastatic diseases had distinct care and prognosis from non-metastatic diseases, the role of frailty on outcomes of may be different in metastatic and non-metastatic breast cancers. The study cohort was separated into women with metastatic or non-metastatic breast cancer. We further identified the patients with frailty in each population (see below).

Study variables

Endpoints: Primary endpoints were in-hospital mortality. Secondary endpoints were: 1) unfavorable discharge, defined as discharged to nursing home or long-term facility; 2) prolonged length of hospital stay (LOS), defined as ≥75th LOS of the study cohort; and 3) total hospital cost.

Assessment of frailty: For each hospitalization, the medical history in the electronic records of the database were extracted and checked. To identify women with frailty, we utilized the Hospital Frailty Risk Score (HFRS), a novel algorithm developed by Gilbert et al. [21] to identify characteristics of frailty from administrative data, which is based on a broad set of ICD diagnostic codes to surrogate the conditions in frailty including codes for volume depletion, chronic pulmonary disease and heart failure...etc. The complete items and detailed codes that HFRS consists of were documented elsewhere [21]. The algorithm has been validated and used in various clinical settings among a number of different countries [22-25]. In the present study, women with a HFRS≥5 were classified as being frail, whereas women with a HRFS<5 were classified as non-frail.

Covariates: Demographic data collected from the NIS database included age, race, household income, insurance status (primary payer), admission type (elective or emergent) were extracted from the NIS database. Clinical data included obesity, active tobacco use, major comorbidities, and severity of comorbidity assessed by the Charlson Comorbidity Index (CCI), and were also identified through ICD-9 and ICD-10 codes. Hospital-related characteristics (bed size, location/teaching status, and hospital region) were extracted from the database in accordance with other studies using the NIS database in the medical literature.

Statistical analysis

Descriptive statistics were presented as number (n) and weighted percentage (%), or mean ± standard error (SE). Women of metastatic breast cancer were propensity score (PS) matched at a ratio of case (frail): control (non-frail) = 1:1 according to variables with significant results, including age, race, insurance status, admission type, obese, active tobacco use, ischemic heart disease, congestive heart failure, diabetes, cerebrovascular disease, chronic pulmonary disease, severe liver disease, moderate or severe renal disease, rheumatic disease, CCI, hospital bed size, and hospital location/teaching status (Supplementary Table 1). Similarly, women of non-metastatic breast cancer were PS matched according to age, race, household income, insurance status, admission type, obese, active tobacco use, ischemic heart disease, congestive heart failure, diabetes, cerebrovascular disease, chronic pulmonary disease, severe liver disease, moderate or severe renal disease, rheumatic disease, CCI, hospital location/teaching status, and hospital region. For comparisons between groups, *p*-values were calculated using PROC SURVEYFREQ and SURVEYREG for categorical and continuous data, respectively. Univariate and multivariable logistic regression models were performed using PROC SURVEYLOGISTIC to determine the factors associated with in-hospital mortality, unfavorable discharge, and prolonged LOS. Linear regression was conducted to identify the factors associated with total hospital cost (per thousand US dollars). Multivariable regression analysis adjusted for variables that were significant in the univariate model. In addition, stratified analyses on the association between frailty and in-hospital mortality by age groups were performed. Since the NIS database covers a 20% sample of the USA annual in-patient admissions, weighted samples (DISCWT), stratum (NIS_STRATUM), and cluster (HOSPID) were used to produce national estimates for all analyses, as suggested by the NIS database guidelines. All analyses were 2-sided, and values of $P<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

The selection process for study cohort is shown in **Figure 1**. A total of 177,170 women who hospitalized for breast cancer were identified in the period during 2005 and 2018 in the NIS database. After excluding patients with missing data of age (n = 56), those <40 years old (n = 12,279), with breast cancer *in situ* (n =

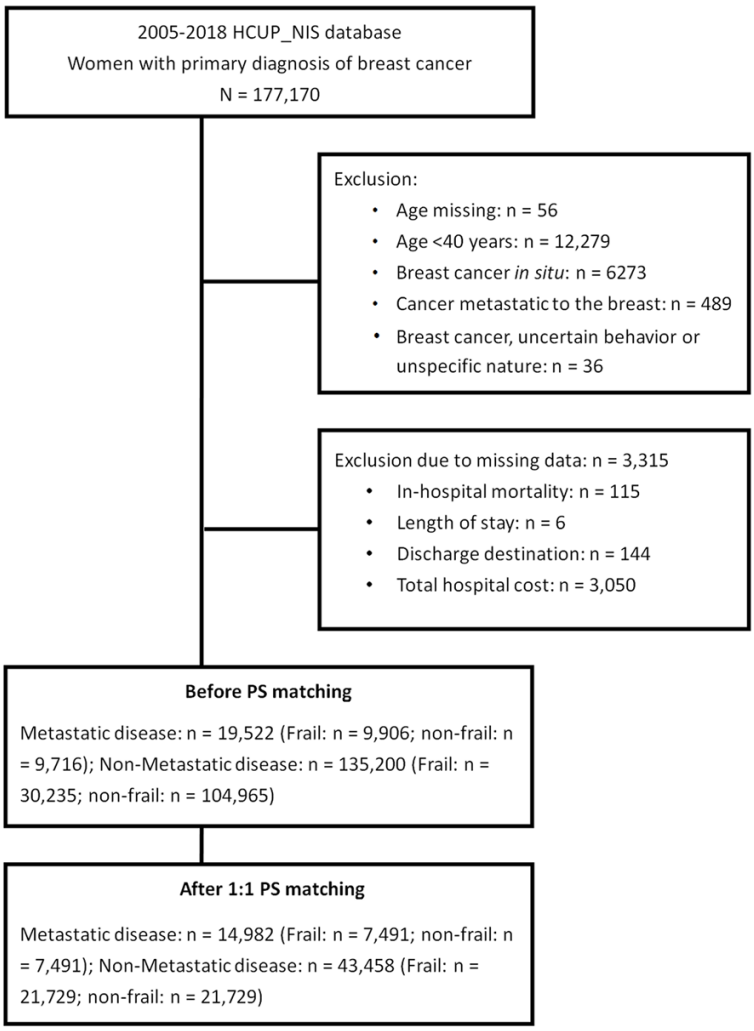

Figure 1. Flow diagram of patient selection.

6,273), with cancer metastatic to the breast (n = 489), with uncertain cancer behavior/unspecific nature (n = 36), and without records of complete information on in-patient outcomes (n = 3,315), a total of 154,772 women were included as the primary cohort. Amongst, 19,522 had metastatic and 135,200 had non-metastatic breast cancer.

After matching, there remained 58,440 women in the study cohort, including 14,982 women with metastatic and 43,458 with non-metastatic breast cancers (**Figure 1**).

Characteristics of women with breast cancer hospitalized between 2005 and 2018

Patient outcomes, demographic and clinical characteristics, and hospital information are summarized in **Table 1**. After matching, mean age of women with metastatic breast cancer and non-metastatic breast cancer was 63.0 and 64.9 years, respectively. Mean total hospital cost was 45.2 and 39.1 thousand US dollars, respectively. Among women with metastatic disease, most of the characteristics were balanced between the case and control groups, except for hospital region. Among women with non-metastatic disease, the proportion of active tobacco use, cerebrovascular disease, chronic pulmonary disease, and hospital bed size were still significantly different between the case and control groups (**Table 1**).

Outcomes of women with breast cancer hospitalized between 2005 and 2018

Outcomes of the hospitalizations were listed in **Table 2**. For patients with metastatic and non-metastatic disease, in-hospital mortality was 15.5% and 1.1%; percentage of prolonged LOS was 48.3% and 12.4%; unfavorable discharge was 21.0% and 6.9%; and total hospital cost was 44,665.8 and 40,156.7 dollars, respectively. Compared to non-frail women, frail women had a higher frequency of worse outcomes with respect to mortality, prolonged LOS, unfavorable discharge, and greater total cost, regardless of status of metastasis (all, P<0.001) (**Table 2**).

Associations between frailty and in-hospital outcomes in women with breast cancer

Associations between HFRS-defined clinical frailty and in-hospital mortality or unfavorable discharge are shown in **Table 3**. For patients with metastatic breast cancer, after adjustment for relevant confounders in the multivariate analyses, the results showed frail women had a significantly higher risk of in-hospital mortality (adjusted odds ratio [aOR] = 1.55; 95% CI: 1.35-1.78), unfavorable discharge (aOR

Table 1. Characteristics of women hospitalized with breast cancer after PS matching

Characteristics	Metastatic				Non-Metastatic			
	Total (n = 14,982)	Frailty		*P*-value	Total (n = 43,458)	Frailty		*P*-value
		Yes (n = 7,491)	No (n = 7,491)			Yes (n = 21,729)	No (n = 21,729)	
HFRS	7.4±0.09	12.9±0.10	2.0±0.02	**<0.001**	6.2±0.04	11.0±0.05	1.4±0.01	**<0.001**
Demography								
Age, year	63.0±0.12	63.2±0.16	62.9±0.16	0.281	64.9±0.10	65.1±0.13	64.8±0.11	0.067
40-49	2288 (15.2)	1139 (15.2)	1149 (15.2)	0.899	6659 (15.3)	3307 (15.2)	3352 (15.4)	0.864
50-59	4100 (27.4)	2028 (27.0)	2072 (27.7)		9725 (22.4)	4850 (22.3)	4875 (22.5)	
60-69	4075 (27.2)	2046 (27.3)	2029 (27.1)		10611 (24.4)	5318 (24.5)	5293 (24.3)	
70-79	2754 (18.4)	1386 (18.6)	1368 (18.3)		8575 (19.7)	4330 (19.9)	4245 (19.6)	
80+	1765 (11.8)	892 (11.9)	873 (11.7)		7888 (18.1)	3924 (18.1)	3964 (18.2)	
Race								
White	8652 (64.5)	4337 (64.6)	4315 (64.3)	0.894	28135 (74.4)	14069 (74.4)	14066 (74.4)	0.539
Black	2784 (20.7)	1379 (20.5)	1405 (21.0)		5333 (14.1)	2641 (14.0)	2692 (14.2)	
Hispanic	1142 (8.5)	578 (8.6)	564 (8.4)		2422 (6.4)	1202 (6.4)	1220 (6.5)	
Others	843 (6.3)	418 (6.2)	425 (6.3)		1919 (5.1)	990 (5.2)	929 (4.9)	
Missing data	1561	782	779		5649	2827	2822	
Household income								
Quartile 1	4251 (29.0)	2130 (29.1)	2121 (29.0)	0.999	10478 (24.5)	5196 (24.3)	5282 (24.7)	0.682
Quartile 2	3742 (25.6)	1870 (25.6)	1872 (25.7)		10384 (24.3)	5186 (24.3)	5198 (24.4)	
Quartile 3	3428 (23.4)	1717 (23.4)	1711 (23.4)		10551 (24.7)	5286 (24.7)	5265 (24.7)	
Quartile 4	3199 (21.9)	1603 (21.9)	1596 (21.9)		11260 (26.5)	5672 (26.7)	5588 (26.2)	
Missing data	362	171	191		785	406	379	
Insurance status								
Medicare/Medicaid	8874 (59.4)	4429 (59.3)	4445 (59.5)	0.982	25435 (58.6)	12668 (58.4)	12767 (58.8)	0.377
Private including HMO	4878 (32.6)	2447 (32.7)	2431 (32.5)		16527 (38.1)	8286 (38.2)	8241 (38.0)	
Self-pay/no-charge/other	1195 (8.0)	597 (8.0)	598 (8.0)		1447 (3.3)	748 (3.5)	699 (3.2)	
Missing data	35	17	18		49	27	22	
Admission type								
Emergent	3134 (21.0)	1627 (21.8)	1507 (20.1)	0.143	34927 (80.5)	17494 (80.7)	17433 (80.4)	0.522
Elective	11820 (79.0)	5849 (78.2)	5971 (79.9)		8431 (19.5)	4177 (19.3)	4254 (19.6)	
Missing data	28	15	13		100	58	42	
Obese	847 (5.7)	449 (6.0)	398 (5.3)	0.090	5171 (11.9)	2601 (11.9)	2570 (11.9)	0.946
Active tobacco use	2731 (18.2)	1376 (18.4)	1355 (18.1)	0.612	12970 (29.9)	6329 (29.2)	6641 (30.6)	**0.005**
Major comorbidities								
Ischemic heart disease	741 (5.0)	361 (4.8)	380 (5.1)	0.394	4268 (9.8)	2124 (9.8)	2144 (9.9)	0.735
Congestive heart failure	930 (6.2)	460 (6.2)	470 (6.3)	0.747	2294 (5.3)	1156 (5.3)	1138 (5.3)	0.748
Diabetes	2321 (15.5)	1160 (15.4)	1161 (15.5)	0.913	8796 (20.3)	4413 (20.3)	4383 (20.2)	0.674
Cerebrovascular disease	143 (0.9)	78 (1.0)	65 (0.9)	0.259	491 (1.1)	281 (1.3)	210 (1.0)	**0.001**
Chronic pulmonary disease	1701 (11.3)	840 (11.2)	861 (11.5)	0.633	7507 (17.3)	3666 (16.9)	3841 (17.6)	**0.033**
Severe liver disease	349 (2.3)	179 (2.4)	170 (2.3)	0.586	100 (0.2)	56 (0.3)	44 (0.2)	0.224
Moderate or severe renal disease	456 (3.0)	233 (3.1)	223 (3.0)	0.610	2109 (4.9)	1059 (4.9)	1050 (4.8)	0.736
Rheumatic disease	193 (1.3)	90 (1.2)	103 (1.4)	0.373	1010 (2.3)	529 (2.4)	481 (2.2)	0.142
CCI								
0-1	13080 (87.3)	6533 (87.2)	6547 (87.4)	0.888	36817 (84.7)	18344 (84.4)	18473 (85.0)	0.098
2-3	1557 (10.4)	781 (10.4)	776 (10.4)		5585 (12.9)	2830 (13.1)	2755 (12.7)	
4+	345 (2.3)	177 (2.4)	168 (2.2)		1056 (2.4)	555 (2.6)	501 (2.3)	
Hospital information								
Hospital bed size								
Small	2229 (14.7)	1117 (14.7)	1112 (14.8)	0.490	6608 (15.0)	3240 (14.7)	3368 (15.3)	**0.004**
Medium	3770 (25.3)	1858 (24.9)	1912 (25.7)		10857 (25.2)	5281 (24.5)	5576 (25.9)	
Large	8928 (60.0)	4489 (60.5)	4439 (59.5)		25752 (59.8)	13086 (60.8)	12666 (58.8)	
Missing data	55	27	28		241	122	119	

Hospital location/teaching status								
Rural	1439 (9.7)	710 (9.6)	729 (9.9)	0.788	4307 (10.0)	2151 (10.0)	2156 (10.0)	0.131
Urban non-teaching	5113 (34.2)	2539 (34.0)	2574 (34.3)		14758 (33.9)	7491 (34.5)	7267 (33.3)	
Urban teaching	8375 (56.1)	4215 (56.4)	4160 (55.8)		24152 (56.1)	11965 (55.6)	12187 (56.6)	
Missing data	55	27	28		241	122	119	
Hospital region								
Northeast	3366 (22.9)	1574 (21.4)	1792 (24.3)	**<0.001**	9360 (22.0)	4695 (22.1)	4665 (21.8)	0.678
Midwest	3318 (22.3)	1665 (22.3)	1653 (22.2)		9553 (22.2)	4840 (22.4)	4713 (21.9)	
South	5881 (38.9)	2934 (38.8)	2947 (39.0)		16386 (37.4)	8127 (37.1)	8259 (37.7)	
West	2417 (15.9)	1318 (17.4)	1099 (14.5)		815 9 (18.5)	4067 (18.4)	4092 (18.5)	

CCI, Charlson Comorbidity Index; HFRS, Hospital Frailty Risk Score; HMO, Health Maintenance Organization; PS, Propensity Score; SE, Standard Error. Data are presented as unweighted counts (n) and weighted percentage (%), or mean ± SE. Significant values are shown in bold.

= 1.94; 95% CI: 1.78-2.12), prolonged LOS (aOR = 2.23; 95% CI: 2.07-2.39), and greater total hospital cost (adjusted β = 15.95; 95% CI: 13.83-18.06) than non-frail women. For women with non-metastatic breast cancer, after adjustment, frailty was significantly and independently associated with higher risk of in-hospital mortality (aOR = 2.92; 95% CI: 2.35-3.61), unfavorable discharge (aOR = 2.81; 95% CI: 2.59-3.06), prolonged LOS (aOR = 2.85; 95% CI: 2.66-3.05), and higher total hospital cost (adjusted β = 2.56; 95% CI: 1.57-3.54) (**Table 3**).

Association between frailty and in-hospital mortality stratified by age

The impacts of HFRS-defined frailty on in-hospital mortality stratified by age <50 years, 50 years to <60 years, and ≥60 years are shown in **Table 4**. Frailty was significantly and independently associated with greater risk for in-hospital mortality among all age subgroups. The greatest adverse impact of frailty on mortality was seen in women aged <50 years with non-metastatic disease (aOR = 3.88; 95% CI: 1.95-7.73) (**Table 4**).

Discussion

This study used data from the NIS database of approximately 155,000 women with breast cancer treated in a hospital to examine the effect of frailty on outcomes. Notable findings include that approximately half of women with metastatic disease and one-quarter of women with non-metastatic disease were frail as measured by HFRS. In women with metastatic disease, frailty was associated with a 55% increased in-hospital mortality, and about doubled risks of unfavorable discharge and prolonged LOS. In women with non-metastatic disease, frailty was still strongly associated with increased risk for worse outcomes. Furthermore, the greatest adverse impact of frailty was seen in women <50 years of age who had non-metastatic diseases.

In this study, we identified frailty using the HFRS, which was developed with a focus on persons in acute care settings using electronic hospital records [21]. It is important to note that there are other commonly used instruments for determining frailty, for example, the Fried frailty phenotype [8, 9], the 30-item frailty index, 40-item frailty index, modified frailty index (mFI), John Hopkins Adjusted Clinical Groups index, and Driver's tool [10]. HFRS showed only a moderate agreement to the Rockwood Frailty Index (Pearson's correlation coefficient 0.41, 95% CI: 0.38-0.47) [21]. HFRS has been validated in various patient groups, including patients with cardiovascular disease [22], patients ≥75 years who encountered emergency department [23], and patients ≥65 years in various surgical settings [24]. A study of frailty in Chinese cancer patients developed a frailty index based on routine laboratory data (FI-LAB) and established an algorithm (MCP, mortality of cancer patients) to predict 5-year mortality [26]. The FI-LAB was directly correlated with increased risk of death, and the MCP had an area under the receiver operating curve (AUC) of 0.691 for predicting 5-year mortality. Despite many studies examining associations of frailty and outcomes, no consensus on a standard instrument to identify frailty has been achieved [4].

A few studies did examine the role of frailty in breast cancer. Williams et al. [15] examined frailty and health-related QoL (HRQoL) in older women with breast cancer. They utilized Caro-

Table 2. Outcomes of women hospitalized with breast cancer after PS matching

	Metastatic				Non-Metastatic			
	Total (n = 14,982)	Frailty		*P*-value	Total (n = 43,458)	Frailty		*P*-value
		Yes (n = 7,491)	No (n = 7,491)			Yes (n = 21,729)	No (n = 21,729)	
Outcomes								
In-hospital mortality	2308 (15.5)	1368 (18.3)	940 (12.7)	**<0.001**	475 (1.1)	352 (1.6)	123 (0.6)	**<0.001**
Prolonged LOS[a,b]	6126 (48.3)	3569 (58.3)	2557 (39.0)	**<0.001**	5309 (12.4)	3790 (17.8)	1519 (7.1)	**<0.001**
Unfavorable discharge[a]	2650 (21.0)	1615 (26.5)	1035 (15.8)	**<0.001**	2960 (6.9)	2136 (10.0)	824 (3.8)	**<0.001**
Total hospital cost	44665.8±579.4	52743.8±946.5	36599.0±508.9	**<0.001**	40156.7±358.6	41443.7±468.4	38869.7±380.9	**<0.001**

LOS, Length of Stay; PS, Propensity; SE, Standard Error. Data were presented as unweighted counts (n) and weighted percentage (%), or mean ± SE. Significant values are shown in bold. [a]Excluded patients who died in the hospital. [b]LOS>5 days.

Table 3. Impact of frailty on outcomes in women hospitalized with breast cancer

Outcomes	Metastatic		Non-Metastatic	
	adjusted[a] OR/β (95% CI)	*p*-value	adjusted[b] OR/β (95% CI)	*p*-value
In-hospital mortality	1.55 (1.35-1.78)	**<0.001**	2.92 (2.35-3.61)	**<0.001**
Prolonged LOS[c,d]	2.23 (2.07-2.39)	**<0.001**	2.85 (2.66-3.05)	**<0.001**
Unfavorable discharge[c]	1.94 (1.78-2.12)	**<0.001**	2.81 (2.59-3.06)	**<0.001**
Total hospital cost (thousand USD)	15.95 (13.83-18.06)	**<0.001**	2.56 (1.57-3.54)	**<0.001**

LOS, Length of Stay; CI, Confidence Interval; OR, Odds Ratio. Significant values are shown in bold. [a]Adjusted for variables with P<0.05 in **Table 1**, including hospital region. [b]Adjusted for variables with P<0.05 in **Table 1**, including active tobacco use, cerebrovascular disease, chronic pulmonary disease, and hospital bed size. [c]Excluded patients who died in the hospital. [d]LOS>5 days.

Table 4. Impact of frailty on in-hospital mortality in women with breast cancer stratified by age

Age, year	Metastatic		Non-Metastatic	
	adjusted[a] OR (95% CI)	*P*-value	adjusted[b] OR (95% CI)	*P*-value
<50	1.95 (1.53-2.48)	**<0.001**	3.88 (1.95-7.73)	**<0.001**
50-60	1.51 (1.27-1.80)	**<0.001**	3.27 (2.03-5.28)	**<0.001**
≥60	1.48 (1.25-1.75)	**<0.001**	2.75 (2.14-3.52)	**<0.001**

CI, Confidence Interval; OR, Odds Ratio. Significant values are shown in bold. [a]Adjusted for variables with P<0.05 in **Table 1**, including hospital region. [b]Adjusted for variables with P<0.05 in **Table 1**, including active tobacco use, cerebrovascular disease, chronic pulmonary disease, and hospital bed size.

lina Frailty Index (CFI) to identify frailty. The results showed pre-frail/frail patients had worse physical function and social roles scores, more fatigue, depression, and more sleep disturbance compared to robust women. Munir et al. [27] used a geriatric assessment tool to develop treatment recommendations for women ≥65 years old with early-stage, non-metastatic breast cancer. Overall, geriatric syndrome may have resulted in significant morbidity among patients received chemotherapy and/or radiotherapy. Mandelblatt et al. [28] examined frailty and long-term mortality in breast cancer patients ≥65 years old. Frailty was identified by 35 baseline illness and function items. The results showed that frail/pre-frail, as compared to robust status, were associated with significantly increased long-term all-cause and breast cancer mortality. A study in women ≥50 years receiving chemotherapy showed there was a longitudinal decline in functional scores, attention and memory with frailty up to 6 months post-treatment [16]. A recent systematic review and meta-analysis by Wang et al. [17] included 13,510 patients reported that prevalence of frailty in breast cancer varied widely, from 5% to 71%, with a pooled prevalence of 43%. However, the prevalence of frailty among breast cancer patients could vary from different instruments measuring frailty.

Our results showed that frailty had greater impact in younger patients. Although frailty is typically considered a condition of older persons, a study by Hanlon et al. [29] showed that it is not uncommon in middle-aged and older adults, and that it can also correlate with significant morbidity. The study included 493,737 persons aged 37 to 73 years from the UK Biobank showed pre-frailty and frailty were significantly associated with mortality for almost all age groups. The results of the present study and those cited above together indicate that frailty is a critical concept when optimizing the care of both younger and older patients with breast cancer.

Our results showed that although frailty was less prevalent in women with non-metastatic diseases, it had a greater adverse impact. This suggests that frailty should be screened for in women with non-metastatic breast cancer.

Strengths and limitations

An important strength is that the data were from a very large database that represents a nationwide population. Also, this is the first study that used the validated HFRS to assess frailty and its impact in breast cancer. On the contrary, similar to other studies using administrative data, the possibility of coding errors may exist. Frailty can result from breast cancer

treatments (e.g., chemotherapy) but since the database lacks detailed information on chemotherapy, this cannot be accounted for. Although important, genetic predisposition for breast cancer (e.g. *BRCA*) also could not be analyzed due to lack of data. Lastly, the NIS did not include data after discharge, thus it was not possible to evaluate late mortality.

Conclusions

In United States women hospitalized with breast cancer, HFRS-defined frailty is a strong predictor for adverse in-patient outcomes in both metastatic and non-metastatic disease. The impact of frailty on adverse outcomes was greater among younger women with non-metastatic disease. Future studies focusing on the interventions toward frailty among breast cancer patients are highly warranted.

Disclosure of conflict of interest

None.

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References

[1] Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J and Cardoso F. Breast cancer. Nat Rev Dis Primers 2019; 5: 66.

[2] Loibl S, Poortmans P, Morrow M, Denkert C and Curigliano G. Breast cancer. Lancet 2021; 397: 1750-1769.

[3] Coughlin SS. Epidemiology of breast cancer in women. Adv Exp Med Biol 2019; 1152: 9-29.

[4] Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G and Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019; 394: 1365-1375.

[5] Minami CA and Cooper Z. The frailty syndrome: a critical issue in geriatric oncology. Crit Care Clin 2021; 37: 151-174.

[6] Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodríguez-Mañas L, Fried LP, Woo J, Aprahamian I, Sanford A, Lundy J, Landi F, Beilby J, Martin FC, Bauer JM, Ferrucci L, Merchant RA, Dong B, Arai H, Hoogendijk EO, Won CW, Abbatecola A, Cederholm T, Strandberg T, Gutiérrez Robledo LM, Flicker L, Bhasin S, Aubertin-Leheudre M, Bischoff-Ferrari HA, Guralnik JM, Muscedere J, Pahor M, Ruiz J, Negm AM, Reginster JY, Waters DL and Vellas B. Physical frailty: ICFSR international clinical practice guidelines for identification and management. J Nutr Health Aging 2019; 23: 771-787.

[7] Campbell AJ and Buchner DM. Unstable disability and the fluctuations of frailty. Age Ageing 1997; 26: 315-318.

[8] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G and McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-156.

[9] Cespedes Feliciano EM, Hohensee C, Rosko AE, Anderson GL, Paskett ED, Zaslavsky O, Wallace RB and Caan BJ. Association of prediagnostic frailty, change in frailty status, and mortality after cancer diagnosis in the Women's Health Initiative. JAMA Netw Open 2020; 3: e2016747.

[10] Di Donato V, Caruso G, Bogani G, Giannini A, D'Oria O, Perniola G, Palaia I, Plotti F, Angioli R, Muzii L and Benedetti Panici P. Preoperative frailty assessment in patients undergoing gynecologic oncology surgery: a systematic review. Gynecol Oncol 2021; 161: 11-19.

[11] Shaw JF, Budiansky D, Sharif F and McIsaac DI. The association of frailty with outcomes after cancer surgery: a systematic review and metaanalysis. Ann Surg Oncol 2022; 29: 4690-4704.

[12] Dai S, Yang M, Song J, Dai S and Wu J. Impacts of frailty on prognosis in lung cancer patients: a systematic review and meta-analysis. Front Med (Lausanne) 2021; 8: 715513.

[13] Jeong JR, Choi JW, Ryu SY and Choe YR. Relationship between frailty and mortality after gastrectomy in older patients with gastric cancer. J Geriatr Oncol 2022; 13: 67-73.

[14] Taylor BL, Xia L, Guzzo TJ, Scherr DS and Hu JC. Frailty and greater health care resource utilization following major urologic oncology surgery. Eur Urol Oncol 2019; 2: 21-27.

[15] Williams GR, Deal AM, Sanoff HK, Nyrop KA, Guerard EJ, Pergolotti M, Shachar SS, Reeve BB, Bensen JT, Choi SK and Muss HB. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer 2019; 27: 2693-2698.

[16] Magnuson A, Lei L, Gilmore N, Kleckner AS, Lin FV, Ferguson R, Hurria A, Wittink MN, Esparaz BT, Giguere JK, Misleh J, Bautista J, Mohile SG and Janelsins MC. Longitudinal relationship between frailty and cognition in patients 50

years and older with breast cancer. J Am Geriatr Soc 2019; 67: 928-936.
[17] Wang S, Yang T, Qiang W, Shen A, Zhao Z, Yang H and Liu X. The prevalence of frailty among breast cancer patients: a systematic review and meta-analysis. Support Care Cancer 2022; 30: 2993-3006.
[18] Jauhari Y, Gannon MR, Dodwell D, Horgan K, Tsang C, Clements K, Medina J, Tang S, Pettengell R and Cromwell DA. Addressing frailty in patients with breast cancer: a review of the literature. Eur J Surg Oncol 2020; 46: 24-32.
[19] Yan CH, Coleman C, Nabulsi NA, Chiu BC, Ko NY, Hoskins K and Calip GS. Associations between frailty and cancer-specific mortality among older women with breast cancer. Breast Cancer Res Treat 2021; 189: 769-779.
[20] Healthcare Cost and Utilization Project (HCUP). Introduction to the Nationwide Inpatient Sample (NIS). Rockville, MD: Agency for Healthcare Research and Quality; 2008.
[21] Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, Arora S, Street A, Parker S, Roberts HC, Bardsley M and Conroy S. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018; 391: 1775-1782.
[22] Nghiem S, Afoakwah C, Scuffham P and Byrnes J. Hospital frailty risk score and adverse health outcomes: evidence from longitudinal record linkage cardiac data. Age Ageing 2021; 50: 1778-1784.
[23] Gilbert T, Cordier Q, Polazzi S, Bonnefoy M, Keeble E, Street A, Conroy S and Duclos A. External validation of the hospital frailty risk score in France. Age Ageing 2022; 51: afab126.
[24] Gunnarsdottir GM, Helgadottir S, Einarsson SG, Hreinsson K, Whittle J, Karason S and Sigurdsson MI. Validation of the Hospital Frailty Risk Score in older surgical patients: a population-based retrospective cohort study. Acta Anaesthesiol Scand 2021; 65: 1033-1042.
[25] Kilkenny MF, Phan HT, Lindley RI, Kim J, Lopez D, Dalli LL, Grimley R, Sundararajan V, Thrift AG, Andrew NE, Donnan GA and Cadilhac DA; Stroke123 Investigators and The AuSCR Consortium. Utility of the hospital frailty risk score derived from administrative data and the association with stroke outcomes. Stroke 2021; 52: 2874-2881.
[26] Jin X, Ren Y, Shao L, Guo Z, Wang C, He Y, Zhou L, Cong M, Ma H, Wang W, Zhou C, Feng Y, Ba Y, Gao J, Lu M, Zhang M, Gu XW, Song C, Xu H and Shi H. Prevalence of frailty and prediction of mortality in Chinese cancer patients using a frailty index-based clinical algorithm-a multicentre study. Cancer Med 2021; 10: 6207-6217.
[27] Munir A, Huws A, Khan S, Sharaiha Y, Holt S and Khawaja S. Geriatric assessment tool application in treatment recommendations for older women with breast cancer. Breast 2022; 63: 101-107.
[28] Mandelblatt JS, Cai L, Luta G, Kimmick G, Clapp J, Isaacs C, Pitcher B, Barry W, Winer E, Sugarman S, Hudis C, Muss H, Cohen HJ and Hurria A. Frailty and long-term mortality of older breast cancer patients: CALGB 369901 (Alliance). Breast Cancer Res Treat 2017; 164: 107-117.
[29] Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R and Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493737 UK Biobank participants. Lancet Public Health 2018; 3: e323-e332.

Supplementary Table 1. Characteristics of women with breast cancer before PS matching

Characteristics	Metastatic				Non-Metastatic			
	Total (n = 19,522)	Frailty		*P*-value	Total (n = 135,200)	Frailty		*P*-value
		Yes (n = 9,906)	No (n = 9,716)			Yes (n = 30,235)	No (n = 104,965)	
HFRS	7.6±0.08	13.4±0.09	1.8±0.02	**<0.001**	3.5±0.03	12.2±0.04	1.0±0.01	**<0.001**
Outcomes								
In-hospital mortality	2938 (15.1)	1733 (17.7)	1205 (12.5)	**<0.001**	918 (0.7)	404 (1.3)	514 (0.5)	**<0.001**
Prolonged LOS[a,b]	7783 (47.0)	4731 (58.7)	3052 (35.8)	**<0.001**	10536 (7.9)	4962 (16.7)	5574 (5.3)	**<0.001**
Unfavorable discharge[a]	3437 (20.8)	2251 (28.0)	1186 (14.0)	**<0.001**	5207 (3.9)	2937 (9.9)	2270 (2.2)	**<0.001**
Total hospital cost (thousand USD)	45.2±0.5	54.2±0.9	36.2±0.5	**<0.001**	39.1±0.3	40.9±0.4	38.6±0.3	**<0.001**
Demography								
Age, years	63.1±0.11	64.5±0.14	61.6±0.14	**<0.001**	61.7±0.08	64.9±0.11	60.8±0.08	**<0.001**
40-49	3081 (15.7)	1300 (13.2)	1781 (18.3)	**<0.001**	28391 (21.0)	4382 (14.5)	24009 (22.9)	**<0.001**
50-59	5293 (27.1)	2458 (25.0)	2835 (29.2)		35390 (26.2)	6880 (22.7)	28510 (27.2)	
60-69	5194 (26.6)	2627 (26.7)	2567 (26.4)		32830 (24.3)	7867 (26.0)	24963 (23.8)	
70-79	3558 (18.3)	1975 (20.2)	1583 (16.3)		23187 (17.1)	6017 (19.9)	17170 (16.4)	
80+	2396 (12.3)	1446 (14.8)	950 (9.8)		15402 (11.4)	5089 (16.9)	10313 (9.8)	
Race				**<0.001**				**<0.001**
White	11153 (63.8)	5703 (64.4)	5450 (63.2)		84537 (72.4)	19027 (72.6)	65510 (72.3)	
Black	3631 (20.8)	1926 (21.7)	1705 (19.8)		14872 (12.8)	4121 (15.7)	10751 (11.9)	
Hispanic	1520 (8.7)	710 (8.0)	810 (9.4)		9376 (8.0)	1754 (6.7)	7622 (8.4)	
Others	1170 (6.7)	515 (5.8)	655 (7.6)		7938 (6.8)	1298 (5.0)	6640 (7.4)	
Missing	2048	952	1096		18477	4035	14442	
Household income				0.214				**<0.001**
Quartile 1	5507 (28.8)	2827 (29.5)	2680 (28.2)		30378 (22.9)	7371 (24.9)	23007 (22.4)	
Quartile 2	4815 (25.3)	2420 (25.3)	2395 (25.3)		31089 (23.4)	7350 (24.7)	23739 (23.1)	
Quartile 3	4503 (23.6)	2244 (23.4)	2259 (23.8)		32576 (24.6)	7396 (24.9)	25180 (24.5)	
Quartile 4	4238 (22.3)	2091 (21.8)	2147 (22.7)		38412 (29.1)	7537 (25.5)	30875 (30.1)	
Missing data	459	224	235		2745	581	2164	
Insurance status				**<0.001**				**<0.001**
Medicare/Medicaid	11392 (58.5)	6161 (63.0)	5231 (54.0)		65454 (48.5)	17838 (59.0)	47616 (45.4)	
Private including HMO	6527 (33.5)	2920 (29.8)	3607 (37.2)		63901 (47.3)	11280 (37.4)	52621 (50.2)	
Self-pay/no-charge/other	1561 (8.0)	705 (7.2)	856 (8.8)		5660 (4.2)	1081 (3.6)	4579 (4.4)	
Missing data	42	20	22		185	36	149	

Admission type				**<0.001**				**<0.001**
Emergent	14439 (74.2)	7878 (80.5)	6561 (67.8)		18776 (13.9)	5729 (19.1)	13047 (12.5)	
Elective	5036 (25.8)	1,907 (19.5)	3,129 (32.2)		11,5995 (86.1)	24,423 (80.9)	91,572 (87.5)	
Missing data	47	21	26		429	83	346	
Obese	1662 (8.5)	1,264 (12.8)	398 (4.1)	**<0.001**	12,178 (9.0)	9,608 (31.7)	2,570 (2.5)	**<0.001**
Active tobacco use	3664 (18.8)	2,151 (21.9)	1,513 (15.6)	**<0.001**	23,070 (17.1)	8,439 (28.0)	14,631 (14.0)	**<0.001**
Major comorbidities								
Ischemic heart disease	1,084 (5.6)	660 (6.7)	424 (4.4)	**<0.001**	8,170 (6.1)	3,346 (11.1)	4,824 (4.6)	**<0.001**
Congestive heart failure	1,383 (7.1)	874 (9.0)	509 (5.3)	**<0.001**	4,025 (3.0)	1948 (6.4)	2,077 (2.0)	**<0.001**
Diabetes	3,274 (16.7)	1,869 (19.0)	1,405 (14.4)	**<0.001**	20,780 (15.4)	7,509 (24.9)	13,271 (12.6)	**<0.001**
Cerebrovascular disease	370 (1.9)	305 (3.1)	65 (0.7)	**<0.001**	1,512 (1.1)	1,302 (4.3)	210 (0.2)	**<0.001**
Chronic pulmonary disease	2,389 (12.2)	1,402 (14.3)	987 (10.1)	**<0.001**	16,495 (12.2)	5,738 (19.0)	10,757 (10.2)	**<0.001**
Severe liver disease	535 (2.7)	363 (3.7)	172 (1.8)	**<0.001**	150 (0.1)	72 (0.2)	78 (0.1)	**<0.001**
Moderate or severe renal disease	1,024 (5.2)	801 (8.2)	223 (2.3)	**<0.001**	3,291 (2.4)	2,024 (6.7)	1,267 (1.2)	**<0.001**
Rheumatic disease	290 (1.5)	172 (1.8)	118 (1.2)	**0.002**	2,358 (1.7)	772 (2.5)	1,586 (1.5)	**<0.001**
CCI				**<0.001**				**<0.001**
0-1	16,306 (83.5)	7,559 (77.1)	8,747 (90.0)		123,402 (91.3)	24,204 (80.0)	99,198 (94.5)	
2-3	2,554 (13.1)	1,756 (17.9)	798 (8.2)		9,968 (7.4)	4,819 (16.0)	5149 (4.9)	
4+	662 (3.4)	491 (5.0)	171 (1.8)		1,830 (1.4)	1,212 (4.0)	618 (0.6)	
Hospital characteristics								
Hospital bed size				**0.008**				0.315
Small	2,942 (14.9)	1,404 (14.1)	1,538 (15.7)		19,992 (14.6)	4,386 (14.3)	15,606 (14.7)	
Medium	4,927 (25.4)	2,475 (25.3)	2,452 (25.4)		32,840 (24.5)	7,464 (24.9)	25,376 (24.3)	
Large	11,589 (59.7)	5,896 (60.6)	5,693 (58.9)		81,727 (61.0)	18,223 (60.8)	63504 (61.0)	
Missing data	64	31	33		641	162	479	
Hospital location/teaching status				**<0.001**				**<0.001**
Rural	1843 (9.5)	879 (9.1)	964 (10.0)		12,289 (9.1)	2,980 (9.9)	9,309 (8.9)	
Urban non-teaching	6,636 (34.0)	3,478 (35.5)	3,158 (32.4)		47,395 (34.9)	10,894 (36.0)	36,501 (34.6)	
Urban teaching	10,979 (56.5)	5,418 (55.4)	5,561 (57.5)		74,875 (55.9)	16,199 (54.1)	58,676 (56.5)	
Missing	64	31	33		641	162	479	
Hospital region				0.052				**<0.001**
Northeast	4,226 (22.0)	2,032 (21.1)	2,194 (23.0)		32,563 (24.6)	6,238 (21.1)	26,325 (25.6)	
Midwest	4,231 (21.8)	2,198 (22.5)	2,033 (21.0)		27,261 (20.4)	6,764 (22.5)	20,497 (19.7)	
South	7,706 (39.2)	3,883 (39.4)	3,823 (39.1)		48,946 (35.9)	11,406 (37.4)	37,540 (35.4)	
West	3,359 (17.0)	1,693 (17.1)	1,666 (16.9)		26,430 (19.2)	5,827 (18.9)	20,603 (19.3)	

Data were presented as unweighted counts (n) and weighted percentage (%), or mean ± SE. [a]Excluded patients who died in the hospital. [b]LOS>5 days. CCI, Charlson Comorbidity Index; HFRS, Hospital Frailty Risk Score; HMO, Health Maintenance Organization; LOS, Length of Hospital Stay; SE, Standard Error. Significant values are shown in bold.