original reports

Development and Validation of a Predictive Model of Severe Fatigue After Breast Cancer Diagnosis: Toward a Personalized Framework in Survivorship Care

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abstract

PURPOSE Fatigue is common and troublesome among breast cancer survivors; however, limited tools exist to predict its risk.

PATIENTS AND METHODS Participants with stage I-III breast cancer were prospectively included from CANTO (ClinicalTrials.gov identifier: NCT01993498), collecting longitudinal data at diagnosis (before the initiation of any cancer treatment) and 1 (T1), 2 (T2), and 4 (T3) years after diagnosis. The main outcome was severe global fatigue at T2 (score ≥ 40/100, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30). Analyses at T3 were exploratory. Secondary outcomes included physical, emotional, and cognitive fatigue (EORTC Quality of Life Questionnaire-FA12). Multivariable logistic regression models retained associations with severe fatigue by bootstrapped Augmented Backward Elimination. Validation methods included 10-fold internal cross-validation, overoptimism-corrected area under the receiver operating characteristic curves, and external validation.

RESULTS Among 5,640, 5,000, and 3,400 patients at T1, T2, and T3, respectively, the prevalence of post-treatment severe global fatigue was 35.6%, 34.0%, and 31.5% in the development cohort. Retained risk factors for severe global fatigue at T2 were severe pretreatment fatigue (adjusted odds ratio *v* no 3.191 [95% CI, 2.704 to 3.767]); younger age (for 1-year decrement 1.015 [1.009 to 1.022]), higher body mass index (for unit increment 1.025 [1.012 to 1.038]), current smoking behavior (*v* never 1.552 [1.291 to 1.866]), worse anxiety (*v* noncase 1.265 [1.073 to 1.492]), insomnia (for unit increment 1.005 [1.003 to 1.007]), and pain at diagnosis (for unit increment 1.014 [1.010 to 1.017]), with an area under the receiver operating characteristic curve of 0.73 (95% CI, 0.72 to 0.75). Receipt of hormonal therapy was a risk factor for severe fatigue at T3 (*v* no 1.448 [1.165 to 1.799]). Dimension-specific risk factors included body mass index for physical fatigue and emotional distress for emotional and cognitive fatigue.

CONCLUSION We propose a predictive model to assess fatigue among breast cancer survivors, within a personalized survivorship care framework. This may help clinicians to provide early management interventions or to correct modifiable risk factors and offer more tailored monitoring and education to patients at risk of severe post-treatment fatigue.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Cancer-related fatigue is one of the most distressing and common post-treatment *sequelae* among survivors of early-stage breast cancer.[1-3] More than 30% of patients with breast cancer experience persistent fatigue symptomatology up to 10 years after treatment completion.[4-7] Cancer-related fatigue can result in substantial adverse physical, psychosocial, and socioeconomic consequences, having a negative impact on overall quality of life.[6] Nevertheless, fatigue is still rarely discussed or proactively managed.[8-10] Cancer-related fatigue is multidimensional in its manifestation, involving physical, emotional, and cognitive dimensions, and most likely multifactorial, being determined by multiple patient characteristics and contextual, psychosocial, and behavioral factors, comorbid conditions, and biologic factors including inflammation, disease characteristics, and antineoplastic therapies.[3]

CONTEXT

Key Objective

This study aimed at identifying patients who have an increased risk of severe and persistent post-treatment fatigue 2 years after diagnosis of early-stage breast cancer.

Knowledge Generated

More than one-in-three patients endured persistent severe post-treatment fatigue. Younger age, higher body mass index, smoking behavior, and concomitant symptom clusters including pretreatment fatigue, anxiety, insomnia, and pain emerged as key risk factors for the development of severe fatigue 2 years after diagnosis. Exploratory models identified receipt of hormonal therapy as an additional risk factor for severe fatigue 4 years after diagnosis.

Relevance

We propose predictive models that may help clinicians to better assess fatigue at diagnosis of breast cancer and provide timely management interventions to those experiencing severe pretreatment fatigue. Our models may also aid the prompt identification of modifiable risk factors and raise awareness to recognize early signs and act timely on worsening symptoms in patients at long-term risk of severe post-treatment fatigue.

Current knowledge of the long-term prevalence, trajectory, and risk factors of breast cancer–related fatigue is still limited,[4,6,11] which hampers our ability to capture its complexity and variability and to clearly identify those at risk of severe fatigue to potentially target with effective interventions. The prospective multicenter CANcer TOxicity (CANTO) cohort (ClinicalTrials.gov identifier: NCT01993498) aims at characterizing toxicities of breast cancer, building on an extensive longitudinal collection of clinical, behavioral, tumor, treatment, and patient-reported outcome data.[12] In this study, we used CANTO to develop and validate a risk model and to generate a predictive tool for long-term severe fatigue.

PATIENTS AND METHODS

Study Design and Patient Selection

We included CANTO participants with stage I-III breast cancer. CANTO collects data at diagnosis of breast cancer (ie, before the initiation of any cancer treatment) and then at 1 (T1), 2 (T2), and 4 (T3) years after diagnosis (corresponding to approximately 3-6 months, 1 year, and 3 years after primary treatment completion, respectively, including breast surgery, chemotherapy and/or radiation therapy). The CANTO study design (ClinicalTrials.gov identifier: NCT01993498) was previously described.[12] All patients provided written informed consent. The study was approved by the ethics committee (ID-RCB:2011-A01095-36,11-039).

Outcome Assessment

The primary outcome of interest was global fatigue, assessed using the multi-item scale of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30[13-15]: Item 10—Did you need to rest? Item 12—Have you felt weak? Item 18—Were you tired? Patients reported fatigue levels on a 4-point Likert scale per item (response values: 1, not at all; 2, a little; 3, quite a bit; and 4, very much). Responses were converted to a 0-100 scale using a standard scoring algorithm,[15] as follows:

$$\text{Raw Fatigue Score} = \frac{(\text{Score Item 10} + \text{Score Item 12} + \text{Score Item 18})}{\text{No. of Items contributed to the scale (No.} = 3)},$$

$$\text{Standardized Fatigue Score} = \frac{(\text{Raw Score} - 1)}{\text{Range§}} * 100,$$

§ is the difference between maximum and minimum possible values of Raw Score. Most items of the EORTC QLQ-C30, including the three items contributing to the global fatigue scale, are scored 1-4, and therefore, the range equals 3.

As secondary outcomes, we assessed the physical, emotional, and cognitive dimensions of fatigue, evaluated by EORTC QLQ-FA12.[16] This is a multidimensional instrument measuring fatigue to be used in conjunction with the core EORTC QLQ-C30. The questionnaire includes five items for physical fatigue (items 1-5), three for emotional fatigue (items 6-8), and two for cognitive fatigue (items 9-10; Data Supplement, online only). In accordance with the scales of the EORTC QLQ-C30, the FA12 scores are transformed to the range of 0-100, following the same scoring algorithm.

For symptom scales, including fatigue, a higher score represents a higher level of symptomatology and/or problems. All standardized fatigue scores were dichotomized using a threshold of ≥ 40/100,[6] indicating clinically relevant fatigue likely affecting patient's daily life and limiting usual activities, therefore requiring dedicated clinicians' attention and prompting supportive care needs.[6,17-20]

Other Variables of Interest

Candidate predictors were selected on the basis of clinical expertise and previous evidence of association with fatigue[3,6] and included clinical features, treatment-related factors, and symptoms (including pretreatment fatigue), defined as in Table 1.[21-24]

Statistical Analysis

Cohort and outcome description. Descriptive statistics summarized distribution of predictors and prevalence of severe fatigue at T1, T2, and T3 in the overall cohort.

Model development. Patients from the 2012 to 2015 enrollment period of the CANTO study were included in the development cohort according to the availability of global fatigue assessments (n = 5,640 at T1, n = 5,000 at T2, and n = 3,400 at T3; complete case; Data Supplement). Potential predictors of severe fatigue were tested in multivariable logistic regression models, using a bootstrapped (No. = 100) Augmented Backward Elimination procedure. Variable selection combines backward elimination on the basis of significance ($P < .05$) and the change-in-estimate criterion, so that nonsignificant variables are retained if their exclusion leads to a relevant change in the parameter estimates of other variables in the model.[25] The main prediction analysis focused on the risk of severe global fatigue at year 2 (T2) after diagnosis. Risk assessment at year 4 (T3) was considered exploratory. We evaluated the discrimination ability of the model by C-statistics, calculating the area under the receiver operating characteristic curve (AUC).

Internal validation. The model was internally validated using 10-fold internal cross-validation and plotting the observed and estimated probability of severe fatigue for each model.[26] To estimate how well the model would perform in external data sets, an overoptimism penalty was subtracted from the C-statistic of the final model.[27]

External validation. Model performance was externally assessed in a validation cohort from a subsequent CANTO enrollment period that extended until 2017 (n = 2,461 at T1, n = 2,101 at T2, and n = 1,469 at T3; Data Supplement). Models previously fitted in the development cohort, including all predictors retained by Augmented Backward Elimination, were applied to patients in the validation cohort. Predictive performance was evaluated by the C-statistic and visually exploring model calibration.

Fatigue risk prediction. To obtain a final, parsimonious model, we fit a logistic regression including a set of predictors retained in the development cohort, which were consistent in the validation cohort.

Sensitivity analyses. A sensitivity analysis was conducted including patients who responded to global fatigue assessments at all time points.

Power considerations. Procedures to calculate the sample size required to obtain a satisfactory outcome prediction were previously published.[28] Briefly, with a binary outcome prevalence of 31%-35%, a minimal sample size of 998 patients was needed to minimize overfitting (expected shrinkage of predictor effects 10% or lower) and to ensure precise estimation of key parameters in the prediction model at T1 (including an absolute difference of 0.05 in the model apparent and adjusted R^2 value). To achieve the same criteria at T2 and T3, at least 665 and 659 participants were required, respectively.[28] To maximize power, model performance was assessed among all patients who had global fatigue assessments available at T1, T2, and T3, respectively.

This study followed the TRIPOD[29] Checklist for Prediction Model Development and Validation. Additional methodological details are provided in the Data Supplement.

Statistical analysis was performed using SAS statistical software Version 9.4. Statistical significance was defined with a two-sided $P < .05$.

RESULTS

Primary Outcome Evaluation: Severe Global Fatigue

Characteristics of the overall population are shown in Table 1 and in the Data Supplement by severe global fatigue.

In the development and validation cohorts, respectively, prevalence of severe global fatigue at baseline was 24.3% and 26.7%, reached 35.6% and 38.0% at T1 (ie, closest to primary treatment completion), was substantially unchanged to 34.0% and 35.1% at T2, and remained elevated at 31.5% and 35.9% until T3 (Fig 1).

Reporting severe pretreatment fatigue was a consistent predictor of post-treatment fatigue at all time points (Tables 2 and 3; Data Supplement).

In the main predictive model for severe global fatigue at T2, six other predictors were consistent in the development and validation models. These included younger age (adjusted odds ratio for 1-year decrement 1.015 [95% CI, 1.009 to 1.022]), higher body mass index (BMI; for unit increment 1.025 [1.012 to 1.038]), current smoking behavior (*v* never 1.552 [1.291 to 1.866]), and concomitant symptoms at diagnosis such as worse anxiety (*v* noncase 1.265 [1.073 to 1.492]), insomnia (for unit increment 1.005 [1.003 to 1.007]), and pain (for unit increment 1.014 [1.010 to 1.017]; Table 2; AUC 0.73 [95% CI, 0.72 to 0.75]).

In the exploratory model for fatigue at T3, premenopausal status (*v* postmenopausal 1.325 [1.123 to 1.563]) and receipt of hormonal therapy (*v* no 1.448 [1.165 to 1.799]) surfaced as risk factors for severe fatigue (Table 3; AUC 0.71 [95% CI, 0.70 to 0.72]). Of note, 38.6% and 87.4% of premenopausal women age < 40 and 40 years or older, respectively, reported post-chemotherapy interruption of menses at T3 (< 5% overall received ovarian function suppression), which was not associated with severe fatigue ($P = .914$ and $P = .515$, respectively).

Among treatment-related variables, although the development model retained an association between the receipt

TABLE 1. Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%)

Characteristic	T2, 2 Years After Diagnosis		T3, 4 Years After Diagnosis	
	Development Cohort (n = 5,000)	Validation Cohort (n = 2,101)	Development Cohort (n = 3,400)	Validation Cohort (n = 1,469)
Clinical factors				
Age at diagnosis, years				
Mean (SD)	56.3 (11.2)	56.4 (10.6)	56.7 (10.9)	55.6 (10.6)
Minimum-maximum	22.0-88.0	25.3-83.9	22.0-88.0	25.3-83.9
BMI at diagnosis, kg/m^2				
Mean (SD)	25.8 (5.3)	25.9 (5.4)	25.8 (5.2)	25.6 (5.3)
Missing	16	8	12	3
Menopausal status				
Premenopausal	1,827 (37.2)	786 (37.8)	1,180 (35.4)	595 (40.9)
Postmenopausal	3,085 (62.8)	1,291 (62.2)	2,155 (64.6)	858 (59.1)
Missing	88	24	65	16
Charlson comorbidity index				
0	3,705 (80.0)	1,600 (82.9)	2,551 (80.7)	1,151 (83.6)
≥ 1	926 (20.0)	329 (17.1)	612 (19.3)	225 (16.4)
Missing	369	172	237	93
Marital status				
Not partnered	1,223 (26.3)	411 (20.5)	814 (25.8)	284 (19.9)
Partnered	3,429 (73.7)	1,597 (79.5)	2,339 (74.2)	1,145 (80.1)
Missing	348	93	247	40
Education level				
Primary school	692 (14.6)	231 (11.6)	492 (15.3)	135 (9.5)
High school	2,224 (46.9)	923 (46.2)	1,508 (46.7)	672 (47.3)
College or higher	1,821 (38.4)	842 (42.2)	1,226 (38.0)	613 (43.2)
Missing	263	105	174	49
Household income, Euros per month				
< 1,500	640 (14.5)	248 (12.4)	425 (14.2)	153 (10.8)
≥ 1,500 to < 3,000	1,768 (40.2)	861 (43.1)	1,199 (40.0)	572 (40.4)
≥ 3,000	1,992 (45.3)	888 (44.5)	1,372 (45.8)	691 (48.8)
Missing	600	104	404	53
Alcohol consumption behavior				
Less than daily	4,157 (85.9)	1,789 (86.8)	2,839 (86.3)	1,263 (87.4)
Daily	680 (14.1)	271 (13.2)	450 (13.7)	182 (12.6)
Missing	163	41	111	24
Tobacco use behavior				
Current smoker	791 (16.1)	367 (17.7)	515 (15.4)	221 (15.2)
Former smoker	1,065 (21.7)	436 (21.0)	676 (20.3)	331 (22.7)
Never smoker	3,057 (62.2)	1,273 (61.3)	2,145 (64.3)	903 (62.1)
Missing	87	25	64	14
Physical activity (MET-h per week)				
Median (Q1-Q3)	14.0 (0.0-40.0)	14.5 (0.0-40.0)	16.0 (0.3-40.0)	14.0 (0.0-36.0)
Missing	215	83	148	35

(continued on following page)

TABLE 1. Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%) (continued)

Characteristic	T2, 2 Years After Diagnosis: Development Cohort (n = 5,000)	T2, 2 Years After Diagnosis: Validation Cohort (n = 2,101)	T3, 4 Years After Diagnosis: Development Cohort (n = 3,400)	T3, 4 Years After Diagnosis: Validation Cohort (n = 1,469)
Tumor stage				
Stage I	2,535 (50.7)	1,042 (49.9)	1,787 (52.6)	761 (52.1)
Stage II	1,994 (39.9)	838 (40.2)	1,352 (39.8)	557 (38.2)
Stage III	467 (9.3)	207 (9.9)	258 (7.6)	142 (9.7)
Missing	4	14	3	9
Tumor subtype				
HR+ HER2+	520 (10.5)	215 (10.3)	358 (10.6)	155 (10.6)
HR+ HER2–	3,821 (77.0)	1,597 (76.2)	2,607 (77.2)	1,112 (75.9)
HR– HER2+	201 (4.0)	82 (3.9)	128 (3.8)	63 (4.3)
HR– HER2–	422 (8.5)	203 (9.7)	284 (8.4)	135 (9.2)
Missing	36	4	23	4
Treatment-related factors				
Axillary surgery				
None or sentinel node biopsy	3,050 (61.0)	1,431 (68.1)	2,128 (62.6)	988 (67.3)
Dissection	1,950 (39.0)	670 (31.9)	1,272 (37.4)	481 (32.7)
Breast cancer surgery				
Conservative	3,684 (73.7)	1,572 (74.8)	2,568 (75.5)	1,107 (75.4)
Mastectomy	1,316 (26.3)	529 (25.2)	832 (24.5)	362 (24.6)
Chemotherapy				
No	2,358 (47.2)	999 (47.5)	1,678 (49.4)	694 (47.2)
Yes	2,642 (52.8)	1,102 (52.5)	1,722 (50.6)	775 (52.8)
Radiotherapy				
No	437 (8.7)	132 (6.3)	293 (8.6)	108 (7.4)
Yes	4,561 (91.3)	1,969 (93.7)	3,106 (91.4)	1,361 (92.6)
Missing	2	0	1	0
Hormonal therapy				
No	889 (17.8)	361 (17.2)	610 (17.9)	253 (17.2)
Yes	4,111 (82.2)	1,740 (82.8)	2,789 (82.1)	1,216 (82.8)
Missing	0	0	1	0
Anti-HER2 therapy				
No	4,429 (88.6)	1,827 (87.0)	3,012 (88.6)	1,265 (86.1)
Yes	571 (11.4)	274 (13.0)	388 (11.4)	204 (13.9)
Symptoms				
Anxiety				
Noncase	1,865 (39.0)	829 (41.8)	1,289 (39.6)	571 (40.3)
Doubtful	1,261 (26.4)	515 (26.0)	867 (26.6)	364 (25.7)
Case	1,654 (34.6)	638 (32.2)	1,101 (33.8)	483 (34.1)
Missing	220	119	143	51
Depression				
Noncase	3,926 (82.0)	1,638 (82.6)	2,716 (83.3)	1,172 (82.5)
Doubtful	527 (11.0)	220 (11.1)	328 (10.1)	155 (10.9)
Case	332 (6.9)	125 (6.3)	216 (6.6)	93 (6.5)
Missing	215	118	140	49

(continued on following page)

TABLE 1. Distribution of Cohort Characteristics at 2 Years and 4 Years After Diagnosis, No. (%) (continued)

Characteristic	T2, 2 Years After Diagnosis		T3, 4 Years After Diagnosis	
	Development Cohort (n = 5,000)	Validation Cohort (n = 2,101)	Development Cohort (n = 3,400)	Validation Cohort (n = 1,469)
Insomnia				
Mean (SD)	42.4 (33.2)	43.3 (33.4)	41.2 (32.7)	43.5 (32.9)
Missing	193	88	121	45
Pain				
Mean (SD)	15.4 (21.2)	15.1 (20.5)	14.9 (21.0)	15.4 (20.8)
Missing	160	82	103	39
Hot flashes				
No	3,441 (71.8)	1,358 (69.4)	2,354 (72.5)	951 (68.2)
Yes	1,354 (28.2)	600 (30.6)	893 (27.5)	443 (31.8)
Missing	205	143	153	75

NOTE. Self-reported physical activity assessed by Global Physical Activity Questionnaire-16; Anxiety and Depression scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21); Insomnia and Pain assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; Hot flashes assessed by the Common Terminology Criteria for Adverse Events—CTCAE-v 4.0 (yes = any grade). Approximately 22% and 18% among professionally active women in this cohort had not returned to work 2 and 4 years after diagnosis, respectively.

Abbreviations: BMI, body mass index; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MET-h, metabolic equivalent of task hour; Q, quartile; SD, standard deviation.

of chemotherapy and severe fatigue at year 1 (T1), closest to completion of primary treatment (adjusted odds ratio *v* no 1.270 [95% CI, 1.099 to 1.466]; Data Supplement), this did not seem to persist in later time-point models. By contrast, hormonal therapy represented a significant correlate of severe global fatigue in development models at T2, approximately 1 year into hormonal therapy, and was confirmed as a significant predictor of fatigue at T3, after a longer course of treatment, approximately 3 years.

Model β coefficients for regression equations are presented in Tables 2 and 3. The Data Supplement shows model calibration plots.

Secondary Outcomes Evaluation: Fatigue Dimensions

Prevalence of severe fatigue dimensions followed similar patterns to that of global fatigue, except for emotional fatigue, which tended to progressively improve (Fig 1). Consistent with global fatigue, there was a close relationship between reporting severe pretreatment fatigue and concomitant pain at diagnosis with each of the three dimensions, and chemotherapy was retained as a risk factor for all dimensions of fatigue at T1 in the development cohort. Dimension-specific predictors at all time points included higher BMI for physical fatigue and emotional distress for emotional and cognitive fatigue (Data Supplement).

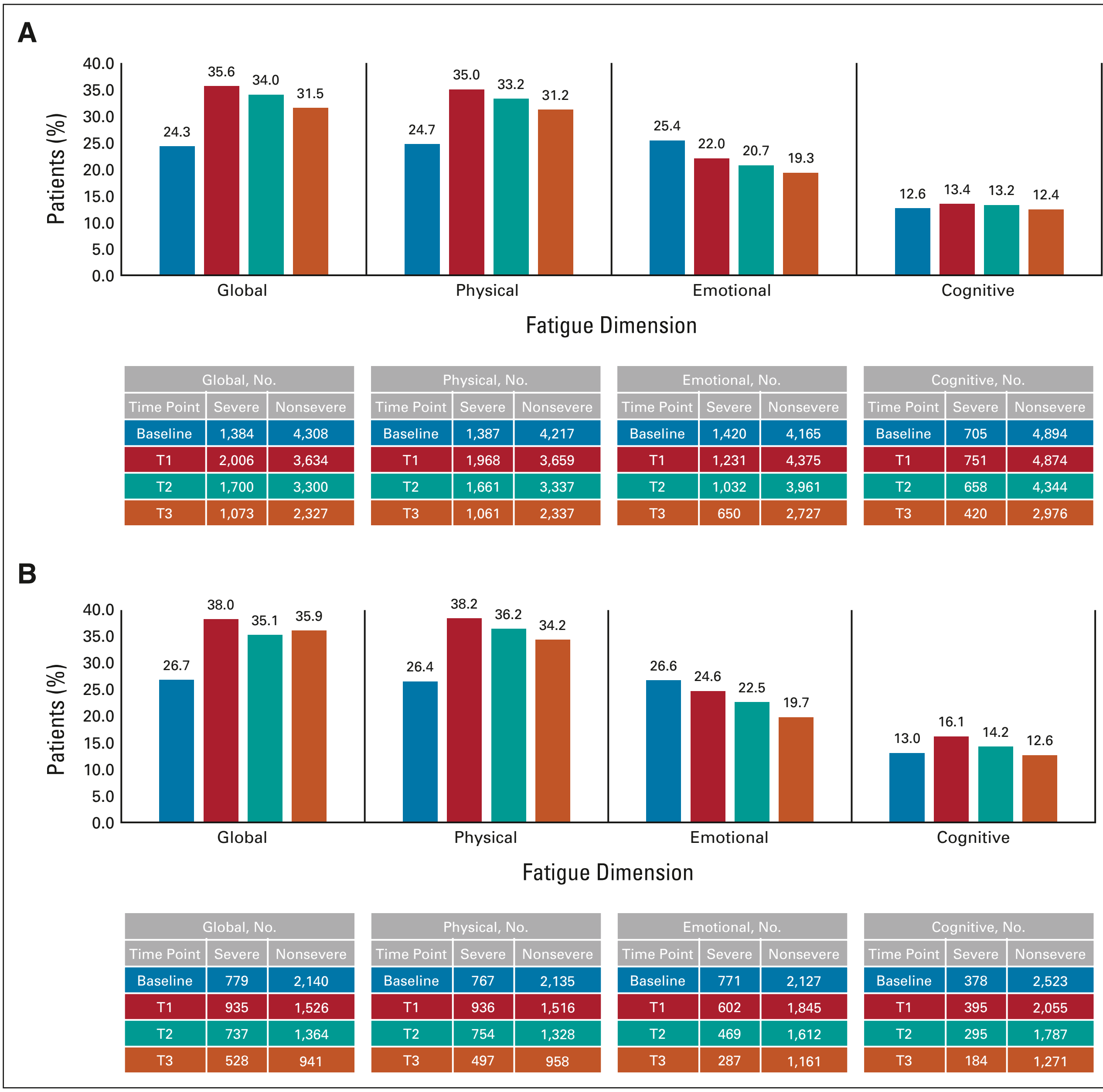
Sensitivity Analyses

The impact of treatment-related variables on fatigue was consistent in sensitivity analyses. In particular, receipt of hormonal therapy was a risk factor for longer-term severe fatigue at T3 (data not shown).

DISCUSSION

Fatigue is a very common side effect among patients with breast cancer, but limited tools exist to predict its risk.[6] About one-in-three patients in CANTO endured persistent, severe fatigue over time. Using the wealth of information of this cohort, we identified clinicobehavioral risk factors and generated a risk model for severe fatigue 2 years after diagnosis of breast cancer, as well as an exploratory model, to provide further insight into risk of severe fatigue 4 years after diagnosis. Dimension-specific risk factors were identified.

Our study confirms and expands the knowledge about relevant risk factors for severe fatigue in survivors of breast cancer.[3,6,11,30-35] Across global and fatigue dimensions, pretreatment fatigue represented the strongest and most consistent predictor. Pretreatment fatigue may set the stage for elevated fatigue even years after treatment completion, because of a disruption in biologic, psychologic, or behavioral mechanisms that exist before treatment onset.[3,4,36-39] Younger age, and, accordingly, premenopausal status, also emerged as risk factors, as previously shown.[5,36,40] In addition, a vulnerable phenotype was represented by patients with high concomitant symptom burden at diagnosis, experiencing several other frequently reported correlates of fatigue, such as sleep disturbances,



A

Global, No.			Physical, No.			Emotional, No.			Cognitive, No.		
Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere
Baseline	1,384	4,308	Baseline	1,387	4,217	Baseline	1,420	4,165	Baseline	705	4,894
T1	2,006	3,634	T1	1,968	3,659	T1	1,231	4,375	T1	751	4,874
T2	1,700	3,300	T2	1,661	3,337	T2	1,032	3,961	T2	658	4,344
T3	1,073	2,327	T3	1,061	2,337	T3	650	2,727	T3	420	2,976

B

Global, No.			Physical, No.			Emotional, No.			Cognitive, No.		
Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere	Time Point	Severe	Nonsevere
Baseline	779	2,140	Baseline	767	2,135	Baseline	771	2,127	Baseline	378	2,523
T1	935	1,526	T1	936	1,516	T1	602	1,845	T1	395	2,055
T2	737	1,364	T2	754	1,328	T2	469	1,612	T2	295	1,787
T3	528	941	T3	497	958	T3	287	1,161	T3	184	1,271

FIG 1. Prevalence of severe global fatigue and of severe fatigue by dimension over time in (A) development cohort and (B) validation cohort. Baseline represents breast cancer diagnosis.

pain (which may include chronic neuropathic pain further exacerbated by more extensive surgical procedures),[41,42] depression, and anxiety.[3,6] Our results also suggest that several correlates are often shared across distinct fatigue dimensions and over time. However, notable was the closer relationship of physical fatigue with increased BMI and that of emotional and cognitive fatigue with psychologic distress and vulnerability, which highlights a need of examining risk factors in view of their possible dimension-specific effects.[3,6]

There seemed to be variation in the way that treatment-related factors affect fatigue at different stages of survivorship. In the shorter term (T1), we found that the chemotherapy-related impact seems transitory and mostly evident in the aftermath of treatment, in line with previous reports, for example, those focused on cognitive function.[43,44] By contrast, a more marked detrimental association between hormonal therapy and fatigue was confirmed after longer exposure (T3). From a broader perspective, these findings support the notion that the impact of hormonal therapy on quality of life does not seem to taper off over time. The Mind Body Study had nicely shown that hormonal therapy exacerbates an array of treatment-associated symptoms, being likely responsible for the failure to resolve some common chemotherapy-related toxicities.[45] Analogously, we had previously

TABLE 2. Predictive Model of the Risk of Severe Fatigue at 2 Years After Diagnosis

Variable	OR	95% CI	β Coefficient	95% CI	*P*
Severe pretreatment fatigue,[a] yes versus no	3.191	2.704 to 3.767	1.160	0.995 to 1.326	< .0001
Age, continuous (for 1-year decrement)	1.015	1.009 to 1.022	–0.015	–0.021 to –0.0088	< .0001
BMI, continuous (for unit increment)	1.025	1.012 to 1.038	0.025	0.012 to 0.038	.0001
Tobacco use behavior, former versus never	1.243	1.055 to 1.463	0.217	0.053 to 0.381	.009
Tobacco use behavior, current versus never	1.552	1.291 to 1.866	0.440	0.256 to 0.624	< .0001
Anxiety,[b] doubtful case versus noncase	1.063	0.895 to 1.262	0.061	–0.110 to 0.233	.485
Anxiety,[b] case versus noncase	1.265	1.073 to 1.492	0.235	0.070 to 0.400	.005
Insomnia,[a] continuous (for unit increment)	1.005	1.003 to 1.007	0.0048	0.0026 to 0.0070	< .0001
Pain,[a] continuous (for unit increment)	1.014	1.010 to 1.017	0.014	0.010 to 0.017	< .0001
Intercept			–1.445	–1.912 to –0.978	< .0001
AUC (95% CI)			0.73 (0.72 to 0.75)		

Abbreviations: AUC, area under the receiver operating characteristic curve; BMI, body mass index; OR, odds ratio.
[a]Scored according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.[14]
[b]Scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21).[23]

suggested how hormonal therapy seems to attenuate the recovery of patient-reported functions that typically get better over time, including emotional function and future persectives.[7] Data from the present study underscore that some patients receiving hormonal therapy—particularly younger, premenopausal women—may require dedicated attention. This is all the more important in consideration of recently implemented strategies to escalate hormonal therapy by adding ovarian function suppression[46] or extending its duration beyond 5 years.[47-49]

Substantial evidence shows that cancer-related fatigue is underaddressed[3,6,8,50] and that the utilization of strategies to manage this symptom may be suboptimal.[51] In light of the collective research to date, including the present study, we propose a risk-stratified framework of long-term toxicity management, applied to fatigue (Table 4), and an online tool for fatigue risk calculation.[58] We envision a clinical care setting where incoming new patients are systematically screened for fatigue and risk factors at breast cancer diagnosis, before the initiation of any cancer treatment. Some among them would already experience pretreatment fatigue and require the upfront utilization of interventions to treat this symptom.[8,50] By contrast, among patients without severe fatigue at diagnosis, a detailed evaluation of factors included in our models would allow a more personalized approach.[59-61] The models we propose include several modifiable behavioral risk factors for which meaningful interventions exist as well as concomitant symptom clusters that can be specifically treated, in the context of a comprehensive survivorship care model that addresses multiple dimensions of health and health promotion.[62] In addition, among patients who do not report severe pretreatment fatigue, being at risk of long-term post-treatment fatigue may indicate a more attentive assessment. This can help to increase awareness among providers and patients to

TABLE 3. Exploratory Predictive Model of the Risk of Severe Fatigue at 4 Years After Diagnosis

Variable	OR	95% CI	β Coefficient	95% CI	*P*
Severe pretreatment fatigue,[a] yes versus no	2.480	2.022 to 3.042	0.908	0.704 to 1.112	< .0001
Menopausal status, pre- versus postmenopausal	1.325	1.123 to 1.563	0.281	0.116 to 0.446	.0009
Hormonal therapy, yes versus no	1.448	1.165 to 1.799	0.370	0.153 to 0.587	.0008
Anxiety,[b] doubtful case versus noncase	1.137	0.924 to 1.398	0.128	–0.079 to 0.335	.225
Anxiety,[b] case versus noncase	1.460	1.196 to 1.781	0.378	0.179 to 0.577	.0002
Insomnia,[a] continuous (for unit increment)	1.004	1.001 to 1.007	0.004	0.0013 to 0.007	.003
Pain,[a] continuous (for unit increment)	1.016	1.012 to 1.021	0.016	0.012 to 0.020	< .0001
Intercept			–2.018	–2.273 to –1.763	< .0001
AUC (95% CI)			0.71 (0.70 to 0.72)		

Abbreviations: AUC, area under the receiver operating characteristic curve; OR, odds ratio.
[a]Scored according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.[14]
[b]Scored according to the Hospital Anxiety and Depression Scale: noncase (score 0-7), doubtful (8-10), and case (11-21).[23]

TABLE 4. Management of Cancer-Related Fatigue Within a Comprehensive Breast Cancer Survivorship Care Framework

Interventions to Manage Fatigue and to Address Risk Factors and Concurrent Symptoms of Fatigue

For Patients With Fatigue	For Patients With Fatigue or High Risk of Developing Fatigue
Management of fatigue during active treatment Physical activity interventions Initiate exercise programs and/or maintain optimal level of physical activity, combining endurance aerobic and resistance training Rehabilitation: eg, physical therapy Physically based therapies: massage therapy Psychosocial interventions Cognitive behavioral therapy Psychoeducational therapies Mind-body interventions: yoga Nutrition consultation Management of fatigue post-treatment Physical activity interventions Initiate exercise programs and/or maintain optimal level of physical activity, combining endurance aerobic and resistance training Rehabilitation: eg, physical therapy Psychosocial interventions Cognitive behavioral therapy Psychoeducational therapies Supportive expressive therapies Mindfulness-based approaches Mind-body interventions: yoga and acupuncture Nutrition consultation	Correct modifiable risk factors and comorbid factors Reduce excess body weight and obesity Lifestyle interventions for improved energy balance and to pursue weight loss: increase and/or maintain adequate levels of physical activity and/or energy expenditure; Improve nutrition and energy intake Cognitive behavioral therapy Encourage and facilitate smoking cessation Screen for and address concurrent symptoms and treatable contributing factors Emotional distress Cognitive behavioral therapy Mindfulness-based approaches Physical activity Yoga Sleep disturbances Sleep hygiene Cognitive behavioral therapy Mindfulness-based approaches Acupuncture Pain Comprehensive assessment including pain experience, etiology, pathophysiology, and aggravating and alleviating factors Psychosocial support Patient and family and/or caregiver education Nonpharmacologic strategies to be considered on the basis of etiology and pathophysiology: eg, physical and occupational therapy, acupuncture, yoga, and massage Review if concomitant medical causes of fatigue exist and treat them; Consider pharmacologic options to treat symptoms on a case-by-case basis

Increase Awareness, Promote Education, and Facilitate Interdisciplinary Referral and Access to Interventions[8,50,52-57]
Systematically screen and monitor fatigue and its correlates
At initial pretreatment visit
At regular intervals during and after treatment
As clinically indicated
Using a quantitative or semiquantitative assessment
Improve education and counseling directed to patients and their family and caregivers
Inform about known patterns and risk factors for persistent fatigue
Consider management of fatigue as integral part of cancer care
Educate to self-monitor changes in fatigue levels over time
Encourage to be attentive to symptoms that can herald the onset of persistent fatigue or develop in conjunction with fatigue, including endocrine therapy–related symptoms (eg, menopausal symptoms)
Promote self-management skills
Advise to seek medical help if a persistent deterioration of energy levels exists
Activate referral network and facilitate access for timely provision of supportive care interventions as appropriate
Prioritize interdisciplinary management of fatigue: include physical therapy, psychology, psychiatry, and integrative therapies
Consider social intervention support for patients who may struggle with lack of resources to obtain access to interventions

recognize symptoms that can herald the onset of persistent fatigue, or develop in conjunction with it, including endocrine therapy–related menopausal symptoms. Increased awareness may then trigger earlier management and referral and facilitate patient access to supportive care when most needed.[50]

Finally, our study offers inspiration for future research in the field, including indications to design meaningful interventional trials. We highlight priorities such as a need to better assess relevant thresholds discriminating between low versus high predicted risk, to validate effectiveness of preventive interventions, to define optimal frequency of fatigue assessments, and to bridge risk stratification with patient activation toward symptom monitoring and acquisition of self-management skills. Acceptability and interpretability of the model should also be qualitatively explored. Future efforts could also be directed at developing adaptive models that provide a dynamic risk assessment. eHealth might serve well this purpose. Digital tools were used to follow-up patient-reported symptoms, and they were effective in reducing symptom burden and improving health-related quality of life, particularly during or shortly after treatment.[63-67] Nevertheless, although eHealth may potentially facilitate the sustainability of long-term cancer survivorship care, fully automated behavioral intervention technologies for symptom monitoring, real-time feedback, and personalized overview of supportive care options have not consistently improved knowledge, skills, and confidence for self-management among cancer survivors.[68]

The translation of risk prediction into delivery of innovation also comes with several challenges. Model use should integrate clinical judgment to aid decision process, and considerations should be given to issues related to risk communication and incorporation into existing workflows. Social determinants of health should be identified as they may generate disparities in access to interventions and resource utilization, elevating barriers among strata with lower level of health and digital literacy and reduced activation.[69] Notably, 22% and 18% among professionally active women in this cohort had not returned to work 2 and 4 years after diagnosis, respectively, consistent with previous findings.[70,71] The subsequent potential impact on the ability to meet more intense financial demands and on the resources to deal with survivorship-related struggles calls for a need of integrating a social intervention plan into survivorship care models.

Some limitations must be acknowledged. Our models were specifically developed and validated to fit CANTO data and might not be fully generalizable to all cancer populations. CANTO was designed to assess evolution of chronic toxicities among survivors without evidence of active disease, which might influence the trajectory of symptoms. We acknowledge potential for bias because of study termination for patients who experience disease recurrence. Furthermore, patients not providing fatigue assessments at later time points may partly overlap with those at risk of developing severe fatigue (ie, prone to unhealthy behaviors, with lower income, more symptomatic at diagnosis). Reduced retention may further limit generalizability, and therefore, exploratory models at T3 are provided with the caveat of interpreting their outputs with caution.

Strengths include a large cohort size, a prospective and longitudinal design following patients from diagnosis into treatment completion through the long-term survivorship, and evaluation of distinct, nuanced dimensions of fatigue. Models were internally and externally validated, demonstrating transportability and accurate predictions among patients drawn from a different, although related population.[29,72-74] Performance was globally satisfactory,[60,61] and models performed similarly well when validated in external patients, providing acceptable discrimination (AUC = 0.70-0.80).[75] Consistency with previous literature and plausibility of the underlying risk mechanisms and processes suggest that our models are clinically sound rather than solely relying on statistical selection methods. In addition, our models allow identification of modifiable risk factors and treatable correlate symptoms, and this was suggested to be a key feature to prioritize rather than simply pursuing maximization of model precision.[26,76]

In conclusion, we assessed the long-term prevalence and risk factors for severe fatigue up to four years after breast cancer diagnosis. We then propose predictive models that may help clinicians to better assess fatigue at diagnosis and provide timely management interventions to those experiencing severe pretreatment fatigue. Our models may also aid the prompt identification of modifiable risk factors and raise awareness to recognize early signs and worsening symptoms in patients at long-term risk of severe post-treatment fatigue. This framework may be extended to other prevalent toxicities in survivorship care, building on the integration of patient-reported outcomes in clinical practice and the increasing accessibility to digital symptom management solutions.

Better understanding of mechanisms of fatigue, including its underlying biologic underpinnings, and testing of screening and prevention algorithms in clinical care settings are needed to implement efficient risk-stratified management interventions for cancer-related fatigue.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development and Validation of a Predictive Model of Severe Fatigue After Breast Cancer Diagnosis: Toward a Personalized Framework in Survivorship Care

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Consulting or Advisory Role: InformedDNA, Vifor Pharma (I), Ambys Medicines (I), Global Blood Therapeutics (I), GlaxoSmithKline (I), Ionis Pharmaceuticals (I), Akebia Therapeutics (I), Protagonist Therapeutics (I), Regeneron (I), Sierra Oncology (I), Rockwell Medical Technologies Inc (I), Astellas Pharma (I), Gossamer Bio (I), American Regent (I), Disc Medicine (I), Blue Note Therapeutics, Grail
Research Funding: Blue Note Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Related to iron metabolism and the anemia of chronic disease, Up-to-Date royalties for section editor on survivorship (I)
Travel, Accommodations, Expenses: Intrinsic LifeSciences (I)

Ann H. Partridge
Patents, Royalties, Other Intellectual Property: I receive small royalty payments for coauthoring the breast cancer survivorship section of UpToDate
Open Payments Link: https://openpaymentsdata.cms.gov/physician/835197

Fabrice André
Stock and Other Ownership Interests: Pegacsy
Research Funding: AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst), Lilly (Inst), Roche (Inst), Daiichi (Inst)
Travel, Accommodations, Expenses: Novartis, Roche, GlaxoSmithKline, AstraZeneca

Stefan Michiels
Consulting or Advisory Role: IDDI, Sensorion, Biophytis, Servier, Yuhan, Amaris Consulting, Roche

Ines Vaz-Luis
Honoraria: AstraZeneca (Inst), Amgen (Inst), Pfizer (Inst)

No other potential conflicts of interest were reported.