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(Pre)treatment risk factors for late fatigue and fatigue trajectories following radiotherapy for breast cancer

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Abstract

Fatigue is common in breast-cancer survivors. Our study assessed fatigue longitudinally in breast cancer patients receiving adjuvant radiotherapy (RT) and aimed to identify risk factors associated with long-term fatigue and underlying fatigue trajectories. Fatigue was measured in a prospective multicenter cohort (REQUITE) using the Multidimensional Fatigue Inventory (MFI-20) and analyzed using mixed models. Multivariable logistic models identified factors associated with fatigue dimensions at 2 years post-RT and latent class growth analysis identified individual fatigue trajectories. A total of 1443, 1302, 1203 and 1098 patients completed the MFI-20 at baseline, end of RT, after 1 and 2 years. Overall, levels of fatigue significantly increased from baseline to end of RT for all fatigue dimensions ($P < .05$) and returned to baseline levels after 2 years. A quarter of patients were assigned to latent trajectory high (23.7%) and moderate (24.8%) fatigue classes, while 46.3% and 5.2% to the low and decreasing fatigue classes, respectively. Factors associated with multiple fatigue dimensions at 2 years include age, BMI, global health status, insomnia, pain, dyspnea and depression. Fatigue present at baseline was consistently associated with all five MFI-20 fatigue dimensions ($OR_{GeneralFatigue} = 3.81$, $P < .001$). From latent trajectory analysis, patients with a combination of factors such as pain, insomnia, depression, younger age and endocrine therapy had a particularly high risk of developing early and persistent high fatigue years

Abbreviations: BMI, body mass index; CRF, cancer-related fatigue; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (Aaronson et al. 1993); GF/PF/MF/RA/RM, General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Activity, Reduced Motivation; IMRT, intensity-modulated radiation therapy; LCGA, latent class growth analysis; MFI-20, multidimensional fatigue inventory 20 (Smets et al. 1995); RT, radiotherapy.

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after treatment. Our results confirmed the multidimensional nature of fatigue and will help clinicians identify breast cancer patients at higher risk of having persistent/late fatigue so that tailored interventions can be delivered.

KEYWORDS
breast cancer, determinants, fatigue, longitudinal trajectories, radiotherapy

What's new?

A substantial proportion of breast cancer patients who undergo radiotherapy experience fatigue years after treatment completion. Underlying risk factors and trajectories of long-term fatigue among affected patients, however, remain poorly understood. Here, the authors analyzed characteristics of fatigue in radiotherapy-treated breast cancer patients via the Multidimensional Fatigue Inventory (MFI-20), an instrument designed for assessment of multiple fatigue dimensions. Analyses identified pain, insomnia, depression, younger age, baseline fatigue and endocrine therapy as factors associated with different dimensions of long-term fatigue. Patients with multiple factors had significantly increased fatigue risk. The findings could aid in identifying such patients and potentially improve interventions.

1 | INTRODUCTION

Cancer-related fatigue (CRF), defined by Bower et al as a *distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning*,[1] is one of the most common adverse effects reported by breast-cancer survivors. The majority of patients report fatigue during endocrine, chemo- and/or radiotherapy (RT), followed by a significant decrease during the first year after treatment completion.[1-3] Some studies showed moderate to severe fatigue persists months and even years after treatment in breast cancer survivors, with a prevalence of RT-induced fatigue between 25% and 40% 1 to 2 years after treatment.[4-7] These findings suggest that the course of fatigue may differ between subpopulations of breast cancer patients, with some being particularly susceptible to experiencing persistent long-term fatigue.

Most observational studies evaluating fatigue in breast cancer patients have been cross-sectional studies that focused on acute fatigue, with assessments up to 6 months after treatment completion. Only a small proportion evaluated CRF beyond 6 months and, from those, even fewer focused on RT-treated patients.[8-11] More than 20 different instruments have been employed to evaluate CRF, contributing to a large heterogeneity in its measurement.[12] Most studies used single-items or unidimensional rather than multidimensional questionnaires and were therefore unable to capture the multidimensional aspect of fatigue with its distinct fatigue dimensions (eg, mental, physical or emotional fatigue).[5,12]

Previous observational studies that evaluated predictors for long-term fatigue yielded varying results. A few predictors were identified, such as obesity, sleep disturbances, depression and anxiety. Other factors like age, localized symptoms, smoking behavior and pain have been inconsistently reported.[4,13-18] Reasons for the inconsistent results between studies include differences related to treatment modality, disease severity, use of different instruments for measuring CRF and assessment of a limited number of potential fatigue determinants.

Recent studies have attempted to capture the course of CRF in breast cancer patients by modeling individual latent (underlying/unobserved) fatigue trajectories and assessing patient characteristics associated with these trajectories.[16-20] With this approach, it is possible to group patients with a similar longitudinal fatigue course and assign them to a specific fatigue trajectory/class. By doing this, one can achieve a more comprehensive assessment and better understanding of the course of fatigue and its variability between patients. Yet most of the previous studies using this modeling approach were underpowered and assessed relatively few fatigue determinants, thus limiting generalizability of the obtained trajectories as well as comparability between studies.

With the present study, we aimed to assess the longitudinal course of fatigue up to 2 years following RT in a large prospectively recruited breast cancer patient cohort, to validate demographic and treatment risk factors associated with multiple dimensions of long-term fatigue and to identify underlying fatigue trajectories (courses of fatigue) and their association with baseline characteristics.

2 | METHODS

2.1 | Data collection and study population

Data from the REQUITE project was used for our study (www.requite.eu).[21] REQUITE is a multicenter, prospective cohort study which recruited non-metastasized breast, prostate and lung cancer patients before RT in 26 hospitals between April 2014 and March 2017 in seven European countries and the United States. Data from the breast cancer cohort was used for our study (n = 2059). The eligibility criteria included patients with planned adjuvant RT after breast-

conserving surgery. Patients with previous malignancies within 5 years before breast cancer diagnosis and/or with previous radiotherapy to the breast were ineligible. Detailed information on inclusion and exclusion criteria can be found in a previous publication.[21] Patients were followed up for a minimum of 24 months, with baseline measurements before RT and after surgery (±chemotherapy) (t1), at the end of RT (t2), 12 months (t3) and 24 months (t4) after treatment.

2.2 | Outcome measurement

Fatigue was measured using the Multidimensional Fatigue Inventory 20 (MFI-20),[22] which was assessed in seven of nine recruiting centers (73% of the breast cancer patient cohort). The MFI-20 is a previously validated instrument composed of 20 items divided into five fatigue dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. Each dimension consists of four items, each one scored on a five-point Likert scale. The scores for every dimension range from four to 20 points, with higher scores representing higher fatigue levels. According to the manual, only subjects with complete data for a given dimension were included in the fatigue analysis.

2.3 | Other measurements

Data on sociodemographic variables and patient characteristics such as age, educational level, physical activity, body mass index (BMI), comorbidities like diabetes, history of heart disease, hypertension and depression were prospectively collected together with data on disease and treatment-related factors, including histologic type, side of primary tumor, tumor stage, surgery type, endocrine therapy, chemotherapy (neoadjuvant or adjuvant) and data specific to RT treatment like total RT dose, RT boost, fractionation scheme and treatment with IMRT. Data for comorbidities were self-reported by the patient and collected using standardized case report forms.

Quality of life-related measures were collected using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).[23] This instrument is composed of 30 items divided into functional and symptom dimensions. All scores were linearly transformed into normalized values ranging between 0 and 100. For the present study, we included pain, dyspnea, insomnia and global health status from the EORTC QLQ-C30 as well as items for breast and arm symptoms from the EORTC QLQ BR-23,[24] which is specific to evaluate quality of life in breast cancer patients. Age was analyzed in 5-unit increments and EORTC QLQ-C30/BR-23 variables in 10-unit increments.

2.4 | Statistical analyses

Descriptive statistics were calculated for multiple patient characteristics, with mean and SD for continuous variables and proportions for categorical variables. To estimate the prevalence of moderate to severe general fatigue in our sample, we used the defined cut-point of >12 points as in previous studies.[25-27] Patient characteristics at baseline of subjects with available MFI-20 data at 24 months and those lost to follow-up were evaluated for potential differences (see Appendix Table S1).

Given that chemotherapy is associated with increased fatigue levels, we stratified our patients by chemotherapy status at baseline (yes/no). Mixed models were used to compare mean fatigue levels over time for each MFI-20 dimension (see Appendix Table S2). Each dimension was evaluated separately. The Bonferroni correction method was used to account for multiple testing ($P < .0085$) for this part of the analysis. Based on a previous publication, we considered a minimal clinically important difference of two points when comparing mean fatigue scores over time for the five dimensions of the MFI-20.[28]

We used multivariable logistic regression analyses to identify and validate factors associated with the occurrence of fatigue at 2 years for the fatigue dimensions separately. For each of the five fatigue dimensions, the outcome was defined as an MFI-20 score of >12 points and the analyses were stratified by chemotherapy status. We tested a selection of relevant covariates based on previous knowledge. These variables include age, BMI, certain comorbidities, EORTC-C30 factors like overall quality of life and disease and treatment characteristics including tumor stage and specific RT variables like type of fractionation scheme (standard fractionation vs hypofractionation), use of an RT boost and type of RT (conventional vs IMRT). After preselecting the covariates to be included in the initial models, a complete case dataset was used for backward and forward stepwise selection to obtain more parsimoniously reduced models. Given their particular relevance as confounding factors, all final models were adjusted for age and baseline (MFI-20) fatigue status.

For the last objective, we used Latent Class Growth Analysis (LCGA) to explore underlying fatigue trajectories (courses) within our data focusing on general fatigue. This method allows to group patients sharing a similar fatigue course and to assign them to a specific fatigue trajectory/class that best describes their mean fatigue levels over time. The optimal number of classes is not known a priori, but can be hypothesized from previous studies and selected by model comparison. The latent class analysis was divided into four steps, as suggested by previous publications.[29,30] First, we defined the underlying growth models, in this case, one model with fixed effects, one with random intercepts and one with random intercepts and slopes. Second, we run models with increasing number of classes (up to five based on findings from previous publications).[16,17,19] Third, we compared the obtained models using the BIC and the AIC to select the best-fitting models. Fourth, we checked the distribution of subjects within each class to ensure that the selected models only included classes with at least 5% of subjects. In this step we also compared the "entropy" of the models, with higher entropy values representing a better distinction between the classes and a better overall classification based on posterior probabilities.

Factors potentially associated with specific trajectories for the general fatigue dimension based on the best fitting model were assessed using multinomial logistic regression. Variables included in the model were selected from bivariate comparisons at a level of $P < .2$. Results from the multinomial model were considered significant at $P < .05$. Estimates reported for any variable were always adjusted for all other variables included in the regression model.

All statistical analyses were carried out using the statistical software R version 4.1.2 (R core team 2022, Vienna, Austria). Mixed modeling and latent class analysis were carried out using the package "*lcmm*."[31]

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are reported in Table 1. A total of 1443, 1302, 1203 and 1098 breast cancer patients answered the MFI-20 at baseline (t1), end of RT (t2), 12 months (t3) and 24 months after RT (t4) for at least one question of the MFI-20. The prevalence of moderate-severe general fatigue (>12 scores) in our sample was 37%, 50% and 34% at the t1, t2 and t4 time points, respectively. Patients had a median age of 58 years and a mean BMI of 26.8 kg/m^2, with 24.7% being obese (≥30 kg/m^2). The majority (61.9%) of patients received a RT boost and conventional fractionation (65.7%). Most patients had invasive tumors (87.0%) and received endocrine therapy (77.1%), while one third of patients (30.0%) were treated with chemotherapy.

3.2 | Longitudinal course of dimensional fatigue

Figure 1 shows the longitudinal mean fatigue scores stratified by chemotherapy status. In the group without chemotherapy, all dimensions follow a similar longitudinal course, starting with low mean fatigue levels, then having a peak at the end of RT, and finally improving close to baseline levels at 12 and 24 months after treatment completion. Mean baseline fatigue scores varied between the five fatigue dimensions, ranging from 8 to 11 points. Fatigue mean scores at the end of RT were significantly higher than mean scores at baseline and returned to baseline levels at 12 and 24 months for all dimensions (*P*-values <.0085). Nevertheless, none of the previous differences reached the minimal clinically important difference of two points.

In the group with chemotherapy, postchemotherapy mean baseline fatigue scores were higher compared to those in the group without chemotherapy, ranging from 9 to 13 points. Fatigue mean scores at baseline were significantly higher than mean scores at 12 and 24 months for all dimensions, except for mental fatigue. There were no significant differences between baseline and end of RT for any dimension. Differences between baseline and 24 months for physical fatigue and reduced activity reached a minimal clinically important difference of two points.

TABLE 1 Baseline characteristics in the overall breast cancer patient cohort and stratified by general fatigue (score >12/yes vs ≤12/no at 24 months.

	Overall at baseline (N = 1443)	Without general fatigue (score ≤12) at 24 months (N = 663)	With general fatigue (score >12) at 24 months (N = 335)
Country			
France	441 (30.6%)	213 (30.9%)	112 (31.3%)
Germany	209 (14.5%)	123 (17.9%)	50 (14.0%)
Italy	102 (7.1%)	55 (8.0%)	25 (7.0%)
Spain A	202 (14.0%)	84 (12.2%)	61 (17.0%)
Spain B	95 (6.6%)	55 (8.0%)	28 (7.8%)
UK	319 (22.1%)	143 (20.8%)	77 (21.5%)
US	75 (5.2%)	16 (2.3%)	5 (1.4%)
General fatigue at baseline			
No	628 (62.9%)	509 (76.8%)	119 (35.5%)
Yes	370 (37.1%)	154 (23.2%)	216 (64.5%)
Age (years)			
Mean (SD)	58.2 (11.0)	57.9 (10.9)	57.6 (10.7)
Median [Min, Max]	58.0 [23.0, 89.0]	58.0 [23.0, 87.0]	57.0 [31.0, 83.0]
Age categories (years)			
<50	342 (23.7%)	159 (24.0%)	78 (23.3%)
50-59	449 (31.1%)	206 (31.1%)	115 (34.3%)
60-69	429 (29.7%)	202 (30.5%)	94 (28.1%)
≥70	223 (15.5%)	96 (14.5%)	48 (14.3%)
Living status			
Living alone	272 (18.8%)	133 (20.1%)	57 (17.0%)
Not living alone	870 (60.3%)	407 (61.4%)	204 (60.9%)
Missing	301 (20.9%)	123 (18.6%)	74 (22.1%)
Educational level			
Low	233 (16.1%)	107 (16.1%)	55 (16.4%)
Medium	536 (37.1%)	262 (39.5%)	132 (39.4%)
High	408 (28.3%)	199 (30.0%)	87 (26.0%)
Missing	266 (18.4%)	95 (14.3%)	61 (18.2%)
BMI (kg/m^2)			
Mean (SD)	26.8 (5.91)	26.1 (5.07)	27.3 (6.00)
Median [Min, Max]	25.6 [13.1, 65.4]	25.1 [17.3, 47.8]	26.4 [16.9, 52.7]
<25	663 (45.9%)	331 (49.9%)	137 (40.9%)
25-29	417 (28.9%)	198 (29.9%)	95 (28.4%)
≥30	357 (24.7%)	133 (20.1%)	100 (29.9%)
Missing	6 (0.4%)	1 (0.2%)	3 (0.9%)
Smoking status			
Current	265 (18.4%)	113 (17.0%)	64 (19.1%)
Never/former	1178 (81.6%)	550 (83.0%)	271 (80.9%)
Depression			
No	1274 (88.3%)	614 (92.6%)	274 (81.8%)
Yes	169 (11.7%)	49 (7.4%)	61 (18.2%)

TABLE 1 (Continued)

	Overall at baseline (N = 1443)	Without general fatigue (score ≤12) at 24 months (N = 663)	With general fatigue (score >12) at 24 months (N = 335)
Time spent sitting (min/day)			
Mean (SD)	345 (203)	340 (195)	359 (212)
Median [Min, Max]	300 [0, 1380]	300 [0, 1140]	300 [0, 1200]
Missing	313 (21.7%)	138 (20.8%)	91 (27.2%)
Global Health Status/QoL (EORTC QLQ-C30)			
Mean (SD)	68.7 (20.3)	73.0 (19.1)	58.6 (19.2)
Median [Min, Max]	66.7 [0, 100]	75.0 [0, 100]	58.3 [0, 100]
Missing	7 (0.5%)	3 (0.5%)	3 (0.9%)
Pain (EORTC QLQ-C30)			
Mean (SD)	20.6 (24.0)	16.1 (20.3)	30.1 (27.1)
Median [Min, Max]	16.7 [0, 100]	16.7 [0, 100]	33.3 [0, 100]
Missing	5 (0.3%)	3 (0.5%)	1 (0.3%)
Insomnia (EORTC QLQ-C30)			
Mean (SD)	33.5 (31.7)	27.6 (28.4)	45.5 (32.0)
Median [Min, Max]	33.3 [0, 100]	33.3 [0, 100]	33.3 [0, 100]
Missing	19 (1.3%)	11 (1.7%)	3 (0.9%)
Radiotherapy boost			
No	550 (38.1%)	242 (36.5%)	115 (34.3%)
Yes	893 (61.9%)	421 (63.5%)	220 (65.7%)
Fractionation scheme			
Hypofractionation (>2 Gy)	495 (34.3%)	216 (32.6%)	109 (32.5%)
Conventional fractionation (≤2 Gy)	948 (65.7%)	447 (67.4%)	226 (67.5%)
IMRT			
No	936 (64.9%)	442 (66.7%)	218 (65.1%)
Yes	504 (34.9%)	219 (33.0%)	116 (34.6%)
Missing	3 (0.2%)	2 (0.3%)	1 (0.3%)
Histologic type			
In situ	169 (11.7%)	85 (12.8%)	36 (10.7%)
Invasive	1256 (87.0%)	577 (87.0%)	295 (88.1%)
Missing	18 (1.2%)	1 (0.2%)	4 (1.2%)
Surgery type			
Segmentectomy/ quadrantectomy	1047 (72.6%)	491 (74.1%)	256 (76.4%)
Wide local excision	375 (26.0%)	168 (25.3%)	75 (22.4%)
Missing	21 (1.5%)	4 (0.6%)	4 (1.2%)
Endocrine therapy			
No	320 (22.2%)	155 (23.4%)	73 (21.8%)
Yes	1112 (77.1%)	508 (76.6%)	262 (78.2%)
Missing	11 (0.8%)	0 (0%)	0 (0%)
Chemotherapy			
No	987 (68.4%)	456 (68.8%)	208 (62.1%)
Yes	433 (30.0%)	200 (30.2%)	124 (37.0%)
Missing	23 (1.6%)	7 (1.1%)	3 (0.9%)
Tumor-stage[a]			
Tis-T1	1152 (79.8%)	531 (80.1%)	269 (80.3%)
T2-T4	239 (16.6%)	110 (16.6%)	58 (17.3%)
Missing	52 (3.6%)	22 (3.3%)	8 (2.4%)

[a]Data on pathological tumor stage was replaced by clinical tumor stage in case of missing values and available clinical data.

Abbreviations: BMI, body mass index; IMRT, intensity-modulated radiation therapy.

3.3 | Determinants of fatigue dimensions at 2 years

Figure 2 shows the factors associated with late fatigue 2 years after RT for the five MFI-20 dimensions (664 patients without chemotherapy, 324 with chemotherapy). Information on ORs and confidence intervals for all variables and all fatigue dimensions is available in the Appendix Tables S3-S7. Validated predictors of fatigue across multiple fatigue dimensions include age, BMI, fatigue (MFI-20) at baseline, global health status, depression and symptoms like insomnia, pain and dyspnea. Fatigue present already at baseline was associated with all five MFI-20 fatigue dimensions regardless of chemotherapy status (eg, general and physical fatigue at 2 years in patients without chemotherapy: $OR_{GF} = 3.81$, 95% CI: 2.52-5.78 and $OR_{PF} = 3.40$, 95% CI: 2.14-5.40, respectively). Depression was consistently associated with late fatigue for all fatigue dimensions except "reduced motivation," and only in the subgroup of patients without chemotherapy (eg, general and mental fatigue at 2 years in patients without chemotherapy: $OR_{GF} = 2.24$, 95% CI: 1.27-3.96 and $OR_{MF} = 1.98$, 95% CI: 1.06-3.59, respectively). On the other hand, determinants like BMI and dyspnea were significantly associated with general fatigue, physical fatigue and reduced activity, but not with reduced motivation and mental fatigue (eg, association between BMI and physical fatigue and reduced activity at 2 years in patients with chemotherapy: $OR_{PF} = 1.08$, 95% CI: 1.03-1.13 and $OR_{RA} = 1.09$, 95% CI: 1.03-1.16, respectively). Endocrine therapy was associated with reduced motivation at 2 years in patients without chemotherapy ($OR_{RM} = 2.27$, 95% CI: 1.26-4.34).

3.4 | Latent general fatigue trajectories and multinomial class analysis

The LCGA (no random effects) model with four trajectories was selected as the best model (Figure 3). Despite not having the best model fit in comparison with random-effect models with four and five classes, the LCGA model with four classes had better entropy and subject classification (see Appendix Figure S1). Identified trajectories

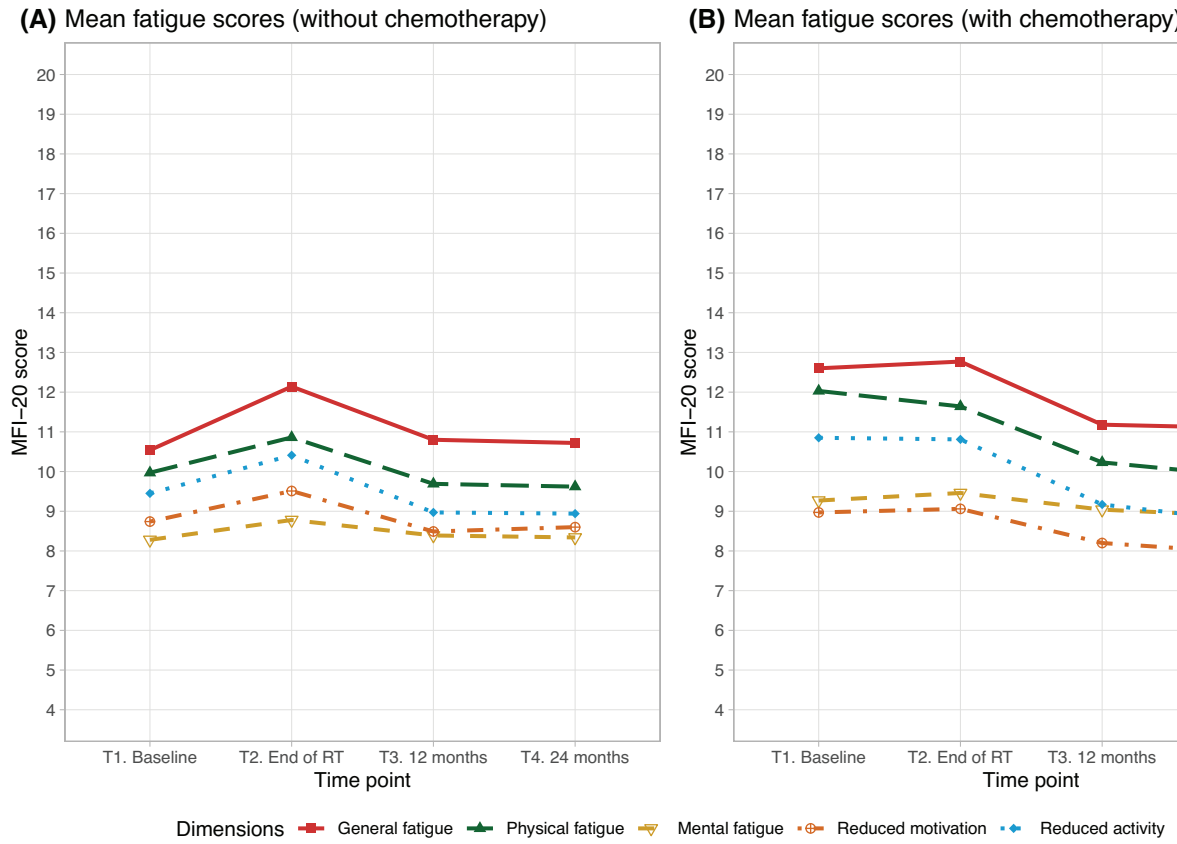

FIGURE 1 Longitudinal mean fatigue scores by fatigue dimension and chemotherapy status in the breast cancer patient cohort from T1 baseline (before radiotherapy [RT] start and after surgery and [if applicable] chemotherapy) to T4 24 months after RT—(A) 1007 breast cancer patients without chemotherapy; (B) 445 breast cancer patients who received chemotherapy.

were classified as high (23.7%), moderate (24.8%), low (46.3%) and decreasing (5.2%) fatigue. For the low, moderate and high fatigue classes, mean fatigue scores started around 7, 11 and 16 points, respectively, then showed a slight temporary increase of 0.5 to 2 points by the end of RT, and finally returned close to baseline levels after 12 and 24 months. Furthermore, the decreasing class showed initial moderate-high fatigue scores, no increase during RT but a substantial decline of approximately six points between baseline and 24 months.

The results from the multinomial logistic regression for the latent trajectory analysis are shown in Table 2. A total of 1494 patients with MFI-20 data for the general fatigue dimension were included in this part of the analyses. From bivariate analyses, 17 variables were selected and included in the final model. Higher insomnia and dyspnea scores were associated with all three fatigue trajectories (high, moderate and decreasing) when compared to the low fatigue class, whereas higher global health status reduced the risk of being in any of these three classes ($OR_{high} = 0.41$, 95% CI: 0.35-0.47, $OR_{moderate} = 0.59$, 95% CI: 0.52-0.67 and $OR_{decreasing} = 0.45$, 95% CI: 0.37-0.55, respectively). Endocrine therapy was significantly associated with a higher risk of being in the high fatigue and in the moderate fatigue class, but not the decreasing class ($OR_{high} = 2.27$, 95% CI: 1.25-4.11 and $OR_{moderate} = 1.68$, 95% CI: 1.07-2.61, respectively). Age was inversely associated with the risk of belonging to the high fatigue class ($OR_{high} = 0.82$, 95% CI: 0.73-0.92), while depression was significantly associated with a higher risk of being in this same class ($OR_{high} = 3.16$, 95% CI: 1.64-6.06). The risk of belonging to the decreasing fatigue class was significantly increased with chemotherapy ($OR_{decreasing} = 2.69$, 95% CI: 1.33-5.42).

4 | DISCUSSION

Fatigue is one of the most prevalent and persistent symptoms reported by breast cancer patients following treatment. Nevertheless, studies assessing the longitudinal course of fatigue in breast cancer patients are scarce and heterogeneous, limiting the identification of relevant risk factors of persistent late fatigue. In the present study, we described the longitudinal course of dimensional fatigue up to 2 years after RT in the large multicenter prospective REQUITE breast cancer patient cohort and decomposed the overall mean fatigue course for general fatigue into four underlying fatigue trajectories/classes. Findings regarding determinants of late fatigue at 2 years were complemented by those associated with persistent high fatigue over 2 years of follow-up, identified through analysis of fatigue trajectories. This contributed to a better understanding of the longitudinal course of fatigue through the identification of

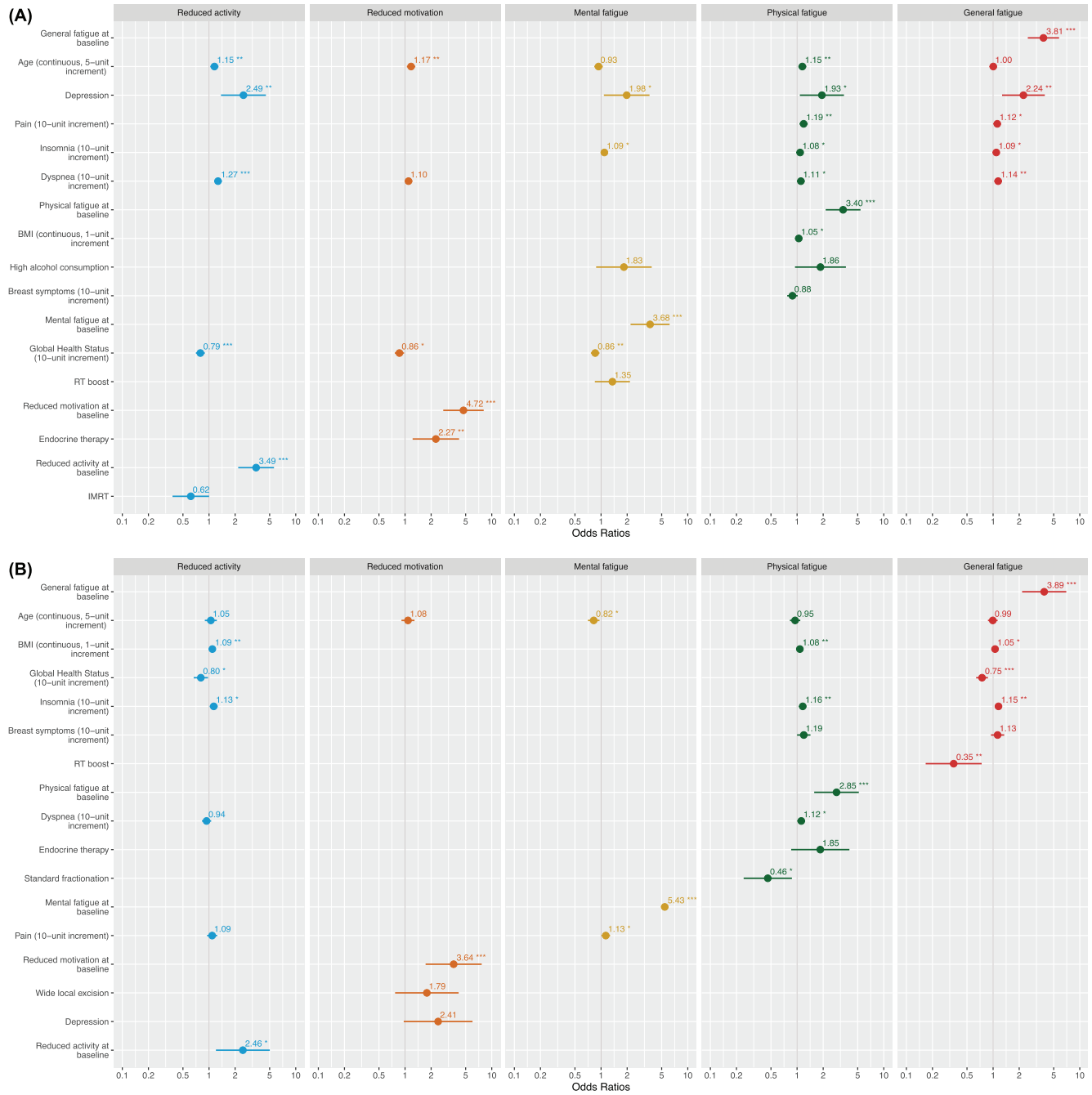

FIGURE 2 Factors associated with late fatigue 2 years after RT for the five MFI-20 dimensions in (A) 664 breast cancer patients without chemotherapy; (B) 324 without chemotherapy. Patients were classified as having fatigue when MFI-20 score were >12 points. **P* < .05, ***P* < .01, ****P* < .001.

distinct fatigue classes linked to subpopulations within our cohort of breast cancer survivors. In addition to this, we also identified baseline factors associated with five fatigue dimensions 2 years after treatment. By this, we expanded our current knowledge on common and specific late fatigue determinants and how these associations might be conditioned by treatment with chemotherapy. This novel comparison allowed us to identify factors such as depression and global health status as factors strongly associated with persistent high general fatigue over time as well as late fatigue dimensions at 2 years.

Regarding fatigue dimensions, previous studies have also observed a similar longitudinal course in breast cancer patients treated with RT, with a transient or sustained increase in fatigue during treatment, and a decrease in fatigue levels after treatment completion.[11,32] In our study, we were able to show distinct longitudinal fatigue patterns when stratifying the patients by chemotherapy

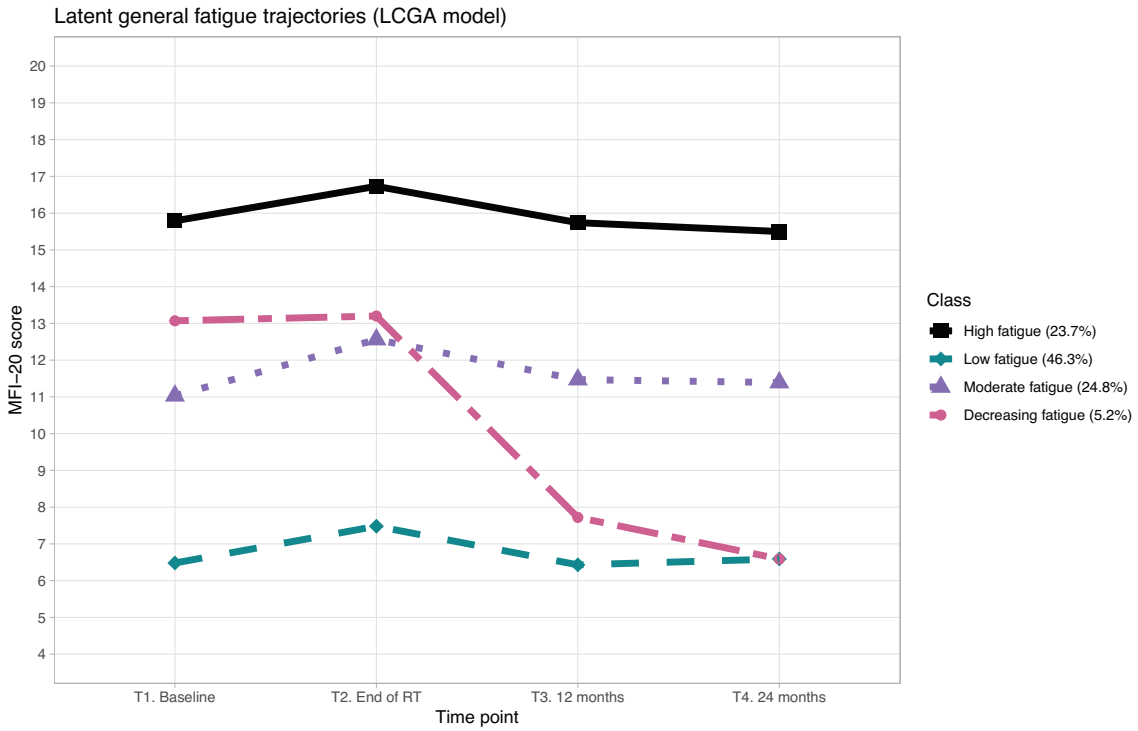

FIGURE 3 Latent fatigue trajectories at four time points for the general fatigue dimension of the MFI-20 in 1494 breast cancer patients.

TABLE 2 Multinomial logistic regression model on latent fatigue trajectories in the breast cancer patient cohort (N = 1271; reference: low fatigue class).

	High fatigue class			Moderate fatigue class			Decreasing fatigue class		
Patient characteristics	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (continuous, 5-unit increment)	0.82	0.73-0.92	**<.001**	0.96	0.88-1.05	.4	1.04	0.88-1.22	.7
BMI (categorical) (ref: <25 kg/m^2)	–	–	–	–	–	–	–	–	–
25-29	1.08	0.67-1.76	.7	0.98	0.69-1.40	>.9	0.84	0.42-1.67	.6
≥30	1.73	1.00-3.02	.051	1.22	0.79-1.89	.4	0.82	0.36-1.90	.6
Depression	3.16	1.64-6.06	**<.001**	1.43	0.82-2.51	.2	1.03	0.32-3.26	>.9
Hypertension	1.41	0.85-2.34	.2	1.18	0.80-1.74	.4	1.04	0.49-2.20	>.9
Smoking status (never/former vs current)	0.96	0.55-1.68	.9	0.82	0.53-1.28	.4	0.58	0.27-1.22	.15
Global Health Status (QLQ-C30) (10-unit increment)	0.41	0.35-0.47	**<.001**	0.59	0.52-0.67	**<.001**	0.45	0.37-0.55	**<.001**
Pain (QLQ-C30) (10-unit increment)	1.18	1.03-1.35	**.016**	1.12	0.99-1.26	.062	0.97	0.81-1.17	.8
Insomnia (QLQ-C30) (10-unit increment)	1.28	1.19-1.38	**<.001**	1.18	1.11-1.26	**<.001**	1.15	1.03-1.28	**.011**
Dyspnea (QLQ-C30) (10-unit increment)	1.33	1.18-1.50	**<.001**	1.17	1.05-1.31	**.004**	1.26	1.08-1.47	**.003**
Arm symptoms (BR23) (10-unit increment)	1.11	0.96-1.28	.15	1.02	0.90-1.15	.8	0.94	0.76-1.17	.6
Breast symptoms (BR23) (10-unit increment)	1.05	0.92-1.21	.5	1.00	0.89-1.12	>.9	1.08	0.87-1.33	.5
Endocrine therapy	2.27	1.25-4.11	**.007**	1.68	1.07-2.61	**.023**	1.40	0.63-3.12	.4
Histologic type (invasive vs in situ)	1.19	0.27-5.20	.8	1.09	0.40-2.97	.9	0.50	0.04-5.57	.6
Chemotherapy	1.27	0.76-2.13	.4	0.87	0.58-1.32	.5	2.69	1.33-5.42	**.006**
Radiotherapy boost	0.63	0.37-1.07	.087	0.82	0.56-1.20	.3	0.94	0.43-2.05	.9
IMRT (vs conventional RT)	0.89	0.55-1.42	.6	1.31	0.92-1.87	.13	1.08	0.56-2.11	.8
Pathologic T-stage (T2-T4 vs Tis-T1)	1.01	0.57-1.77	>.9	1.03	0.66-1.61	.9	0.84	0.38-1.84	.7

status. Women without chemotherapy had a significant increase in fatigue levels during RT, compared to those with previous chemotherapy who did not experience a further increase in their already high fatigue levels. The results are in line with those from a previous study in which fatigue was found *to differ as a function of the type and sequence of treatment*, particularly for those patients receiving chemotherapy and/or RT.[33]

When evaluating fatigue 2 years after RT, baseline fatigue levels were consistently associated with all fatigue dimensions regardless of chemotherapy status. BMI was significantly associated with physical fatigue (both groups) and with reduced activity and general fatigue in the chemotherapy group. A recent study also identified BMI as an important risk factor for global and physical fatigue 2 years after diagnosis, while another study found a positive association between obesity and physical fatigue during and after treatment, also for cognitive fatigue to a lesser degree.[13,20] We also found a strong association between endocrine therapy use and reduced motivation. Our findings show the importance of assessing fatigue from a multidimensional perspective, where different types of fatigue relate to different patient characteristics. Depression and global health status were also associated with late fatigue across most dimensions, predominantly in the group not receiving chemotherapy. These findings agree with previous studies where severe pretreatment fatigue and depression increased the risk of severe fatigue 2 to 2.5 years after diagnosis.[10,17] Fatigue before RT in our cohort of patients is likely due to prior treatments like chemotherapy, and also as a consequence of the tumor itself. Also, the association of depression with multiple fatigue dimensions only for the group without previous chemotherapy supports the idea of determinant effects being strongly affected by cancer treatment. We previously described the longitudinal course of fatigue in patients with and without chemotherapy, with the main difference being elevated baseline levels of fatigue in the chemotherapy group and a marked decline up to 24 months, suggesting an important acute effect of chemotherapy on initial fatigue levels. Similarly, depression, reported by the chemotherapy group at baseline and likely affected by it, might not persist long-term and so would not be correlated with late fatigue in this group of patients. In patients without prior chemotherapy, however, depression might be associated with other external factors that persist over time and which could reflect a chronic mood disorder correlated with some late fatigue dimensions.

Although depression and fatigue usually correlate highly, it is complex to determine the causal mechanisms related to these symptoms in cancer survivors. This is partly because both symptoms may eventually be both cause and effect of each other, as well as being triggered in parallel by pathophysiological mechanisms in common.[34] The pathophysiological mechanisms associated with the occurrence of CRF are still under investigation, with dysregulation of proinflammatory cytokines being one of the most relevant proposed mechanisms so far.[35] Previous research found correlations between depression, insomnia and fatigue, but so far no common inflammatory marker associated with all.[36] In addition, there is evidence that depressive symptoms and the presence of inflammatory markers in breast cancer survivors are independent risk factors for CRF, while depression may act as a mediator between insomnia and fatigue.[37] Although longitudinal studies suggest fatigue as a better predictor of depression than vice versa,[38] as well as of other symptoms such as insomnia and pain,[39] the association between fatigue and depression still seems to be bidirectional, albeit with different predictive power.[34]

Beside chemotherapy, also RT techniques/regimens might play a role as determining treatment factors for fatigue. Here the treated volume but also dose is of major importance. Considering that multiple treatment factors could influence changes in integral dose, the binary variables IMRT and RT boost may not sufficiently capture all the aspects of this possible association. Future research should try to control for additional treatment and disease-related variables and further explore the relationship between integral dose and long-term fatigue.

Based on the hypothesis that some factors may influence the presence of distinct longitudinal fatigue trajectories, we obtained four general fatigue trajectories/classes that describe different mean patterns of fatigue from baseline up to 2 years after RT. The class with the highest number of subjects was the low fatigue group with 46.3%, followed by moderate (24.8%), high (23.7%) and decreasing (5.2%) fatigue groups. These findings are compatible with previous studies on fatigue trajectories, in which (very) low fatigue classes accounted for most of the included patients.[18-20] Three of the trajectories, low, moderate and high fatigue, showed a very similar pattern, with the main difference being the initial fatigue scores and the overall mean fatigue levels over time. It should be noted that the two classes that started with baseline mean fatigue levels >12 (indicating moderate-to-severe fatigue) were the high and decreasing classes only, while the high fatigue class was the only one with mean fatigue scores >12 at T2, T3 and T4. This suggests that, within our sample of patients, those with severe fatigue at baseline (accounting for almost a quarter of the patient cohort) have the highest risk of persistent long-term fatigue, while only a small proportion of patients with high baseline fatigue levels will have a significant decrease in their fatigue levels over time.

From the studies evaluating latent fatigue trajectories in breast cancer patients,[16-20,40] only one study used the MFI-20 to measure fatigue levels over time.[16] Person et al conducted a group-based trajectory analysis in 459 breast cancer patients uncovering three trajectories for the physical and general fatigue dimensions combined. These trajectories followed a pattern similar to the low, moderate and high fatigue trajectories in our study, starting at different baseline fatigue levels, having a transient increase during adjuvant treatment, and returning close to baseline levels after 2 years. The risk of belonging to the *severe, transient-increasing fatigue* class in that study was inversely associated with a better global health status, which is in line with our finding of an inverse association between global health status and the risk of being in the high general fatigue class. On the other hand, Bower et al conducted a latent fatigue analysis in 270 women with stage 0 to stage IIIA breast cancer with five follow-up measurements up to 18 months.[19] They identified a more heterogeneous group of latent classes using the general fatigue subscale of a different multidimensional instrument (Multidimensional Fatigue Symptom Inventory-Short Form, MFSI-SF with 30 items on general fatigue,

physical fatigue, emotional fatigue, mental fatigue and vigor), including *stable high*, *stable low* and *decreasing* classes, which is consistent with our findings, but also an *increasing* and *reactive* class not identified by our model. These differences may be attributable to different inclusion and exclusion criteria between the two study cohorts. In our study, all patients received RT, which means that the effect of this treatment was more similarly distributed among the obtained underlying classes, while in Bower et al, the proportion of patients who had previous RT varied between 50% in the decreasing class and 90% in the reactive class.

Our latent class analysis also validates results from a recent study on long-term fatigue trajectories among breast cancer patients. Vaz-Luis et al conducted a LCGA on 4173 stage I-III breast cancer survivors with fatigue measurements at diagnosis, 1, 2 and 4 years post-treatment using the EORTC QLQ C-30 fatigue subscale. Similar to our cohort, more than 90% of the included patients received RT, around 80% had endocrine therapy, while more than 50% had previous chemotherapy. Their trajectory analysis uncovered three global fatigue trajectories labeled as *high*, *deteriorating* and *low* fatigue, with the *low* and *high* fatigue groups following a similar global pattern to the one we obtained, and also accounting for the majority of patients (60% and 21%, respectively). When evaluating factors in multinomial analysis, BMI (continuous), smoking behavior (current/former vs never), marital status, depression, pain and insomnia were significantly associated with a higher risk of belonging to the high fatigue trajectory, from which depression, pain and insomnia were consistent with our findings. In the case of BMI, we found obesity (BMI > 30 kg/m^2) to be associated with a higher risk of belonging to the high fatigue class (OR = 1.73, 95% CI: 1.00-3.02), also in line with their results.

When comparing the results for general late fatigue from the latent trajectory analyses and that at 2 years, we can see that several common factors such as depression, global health status and symptoms including pain, insomnia and dyspnea were associated with both persistent high and with late fatigue at 2 years. These findings are directly related to the fact that the only latent class with mean fatigue levels >12 at 2 years of follow-up is the high fatigue class, whereas all the other classes have scores <12 at this time-point. Given that our binary outcome uses this threshold to define moderate-severe fatigue, several factors were shared for both models. On the other hand, endocrine therapy and younger age were associated with the high fatigue class but not with general fatigue at 24 months. While the latent class analysis showed a persistent effect of endocrine therapy on general fatigue, the single time-point evaluation at 24 months after RT highlighted reduced motivation as the dimension most strongly associated with such treatment. One explanation for this is differences in patients included in each model. Only patients with available MFI-20 data both at baseline and at 2 years were included in the late fatigue analysis, whereas patients with partial longitudinal data (ie, <4 fatigue measurements) were included in the latent class analysis. The latent general fatigue analysis thus included a more comprehensive group of patients when evaluating persistent fatigue, in comparison to the general late-fatigue analysis focused on a smaller patient cohort (1271 vs 966 after inclusion of covariates, respectively), thus having greater power to identify potential associations between risk factors and longitudinal general fatigue.

Among the strengths of our study are the large sample size, the availability of several patient characteristics including disease and treatment-related factors, the longitudinal nature of the study with prospective long-term follow-up, and the use of a multidimensional questionnaire allowing identifying different factors associated with different fatigue dimensions. However, we acknowledge some limitations. First, about a quarter of patients did not complete the 2-year follow-up MFI questionnaire. When comparing patients with and without MFI data at 2 years, there were significant differences in some variables including BMI, RT and surgical procedures, as well as chemotherapy, so we cannot rule out some degree of attrition bias. However, there were no differences in baseline fatigue scores, suggesting no connection between losses to follow-up and the outcome (Appendix Table S1). Second, some variables identified in the literature as possible fatigue predictors such as socioeconomic status, physical activity and social support were excluded from analyses because of a substantial proportion of missing values (>10%), while others like anemia, hypothyroidism and chronic inflammatory markers were not measured in our cohort of patients and therefore could not be evaluated as possible fatigue predictors. Comorbidities included in the models as dichotomized variables (yes/no), such as depression or hypertension, were assessed using standardized case report forms in patients' interviews. The prevalence for the included comorbidities in our sample might have been under or overestimated. It is also important to mention that LCGA is a data-driven approach dependent greatly on the type of model used and the process of model selection. Trajectories may vary significantly within the same dataset depending on decisions taken. We acknowledge the exploratory nature of this method. Third, given the observational nature of the study, it was not possible to control for external unknown variables that may have a confounding effect on some of the estimates that we obtained.

5 | CONCLUSIONS

We validated several factors associated with the occurrence of multidimensional fatigue 2 years after RT. Some factors such as baseline fatigue levels and depression were associated with all or most fatigue dimensions, while others such as BMI were associated with specific dimensions (eg, physical fatigue), thus corroborating the multidimensional nature of fatigue. Results from LCGA also shed some light on distinct longitudinal fatigue phenotypes and validated factors associated with persistent high fatigue. Patients with a combination of factors such as pain, insomnia, depression, younger age and previous endocrine therapy have a particularly high risk of developing early fatigue but also having persistent high fatigue even years after treatment. These results are relevant for continuing efforts to identify patients at higher risk of persistent late fatigue so that tailored and opportune interventions can be delivered to specific groups of patients.

AUTHOR CONTRIBUTIONS

Juan C. Rosas: Data analysis; wrote original draft; data interpretation; study and data management. **Miguel E. Aguado-Barrera:** Patient enrolment and data collection. **David Azria:** Patient enrolment and data collection. **Erik Briers:** Cancer patient advocates of the REQUITE study. **Rebecca Elliott:** Study and data management. **Marie-Pierre Farcy-Jacquet:** Patient enrolment and data collection. **Alexandra Giraldo:** Patient enrolment and data collection. **Sara Gutiérrez-Enríquez:** Patient enrolment and data collection. **Tiziana Rancati:** Patient enrolment and data collection. **Tim Rattay:** Patient enrolment and data collection. **Victoria Reyes:** Patient enrolment and data collection. **Barry Rosenstein:** Patient enrolment and data collection. **Dirk De Ruysscher:** Patient enrolment and data collection. **Elena Sperk:** Patient enrolment and data collection. **Hilary Stobart:** Cancer patient advocates of the REQUITE study. **Christopher Talbot:** Chief investigators of the REQUITE study; Patient enrolment and data collection. **Ana Vega:** Patient enrolment and data collection. **Begoña Taboada-Valladares:** Patient enrolment and data collection. **Liv Veldeman:** Patient enrolment and data collection. **Tim Ward:** Cancer patient advocates of the REQUITE study. **Adam Webb:** Study and data management. **Catharine West:** Chief investigators of the REQUITE study. **Jenny Chang-Claude:** Study design; wrote original draft; data interpretation. **Petra Seibold:** Study design; wrote original draft; data interpretation; study and data management. All authors reviewed and approved the final manuscript. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

All recruited patients gave written informed consent and the REQUITE study was approved by local ethics committees and registered at www.controlled-trials.com ISRCTN98496463.[21]

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REFERENCES

1. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014;32:1840-1850.
2. Hickok JT, Roscoe JA, Morrow GR, Mustian K, Okunieff P, Bole CW. Frequency, severity, clinical course, and correlates of fatigue in 372 patients during 5 weeks of radiotherapy for cancer. *Cancer*. 2005;104:1772-1778.
3. de Jong N, Candel MJJM, Schouten HC, Huijer Abu-Saad H, Courtens AM. Prevalence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy. *Ann Oncol*. 2004;15:896-905.
4. Servaes P, Gielissen MFM, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. *Psychooncology*. 2007;16:787-795.
5. Abrahams HJG, Gielissen MFM, Schmits IC, Verhagen CAHHVM, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol*. 2016;27:965-974.
6. Schmidt ME, Hermann S, Arndt V, Steindorf K. Prevalence and severity of long-term physical, emotional, and cognitive fatigue across 15 different cancer entities. *Cancer Med*. 2020;9:8053-8061.
7. Noal S, Levy C, Hardouin A, et al. One-year longitudinal study of fatigue, cognitive functions, and quality of life after adjuvant radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:795-803.
8. Battisti NML, Hatton MQ, Reed MWR, et al. Observational cohort study in older women with early breast cancer: use of radiation therapy and impact on health-related quality of life and mortality. *Radiother Oncol*. 2021;161:166-176.
9. Jacobs DHM, Charaghvandi RK, Horeweg N, et al. Health-related quality of life of early-stage breast cancer patients after different radiotherapy regimens. *Breast Cancer Res Treat*. 2021;189:387-398.
10. Geinitz H, Zimmermann FB, Thamm R, Keller M, Busch R, Molls M. Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. *J Cancer Res Clin Oncol*. 2004;130:327-333.
11. Hauth F, De-Colle C, Weidner N, et al. Quality of life and fatigue before and after radiotherapy in breast cancer patients. *Strahlenther Onkol*. 2021;197:281-287.
12. Ruiz-Casado A, Álvarez-Bustos A, de Pedro CG, Méndez-Otero M, Romero-Elías M. Cancer-related fatigue in breast cancer survivors: a review. *Clin Breast Cancer*. 2021;21:10-25.
13. Schmidt ME, Wiskemann J, Schneeweiss A, Potthoff K, Ulrich CM, Steindorf K. Determinants of physical, affective, and cognitive fatigue during breast cancer therapy and 12 months follow-up. *Int J Cancer*. 2018;142:1148-1157.
14. Reinertsen KV, Cvancarova M, Loge JH, Edvardsen H, Wist E, Fosså SD. Predictors and course of chronic fatigue in long-term breast cancer survivors. *J Cancer Surviv*. 2010;4:405-414.
15. Di Meglio A, Havas J, Soldato D, et al. Development and validation of a predictive model of severe fatigue after breast cancer diagnosis: toward a personalized framework in survivorship care. *J Clin Oncol*. 2022;40:1111-1123.
16. Person H, Guillemin F, Conroy T, Velten M, Rotonda C. Factors of the evolution of fatigue dimensions in patients with breast cancer during the 2 years after surgery. *Int J Cancer*. 2020;146:1827-1835.
17. Bower JE, Wiley J, Petersen L, Irwin MR, Cole SW, Ganz PA. Fatigue after breast cancer treatment: biobehavioral predictors of fatigue trajectories. *Health Psychol*. 2018;37:1025-1034.
18. Vaz-Luis I, Di Meglio A, Havas J, et al. Long-term longitudinal patterns of patient-reported fatigue after breast cancer: a group-based trajectory analysis. *J Clin Oncol*. 2022;40:2148-2162. doi:10.1200/jco.21.01958
19. Bower JE, Ganz PA, Irwin M, et al. Do all patients with cancer experience fatigue? A longitudinal study of fatigue trajectories in women with breast cancer. *Cancer*. 2021;127:1334-1344.
20. Bean HR, Diggens J, Ftanou M, Weihs KL, Stanton AL, Wiley JF. Insomnia and fatigue symptom trajectories in breast cancer: a longitudinal cohort study. *Behav Sleep Med*. 2021;19:814-827.
21. Seibold P, Webb A, Aguado-Barrera ME, et al. REQUITE: a prospective multicentre cohort study of patients undergoing radiotherapy for breast, lung or prostate cancer. *Radiother Oncol*. 2019;138:59-67.
22. Smets EM, Garssen B, Bonke B, et al. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39:315-325.
23. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365-376.
24. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14:2756-2768.
25. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie*. 2003;26:140-144.
26. Kuhnt S, Ernst J, Singer S, et al. Fatigue in cancer survivors – prevalence and correlates. *Onkologie*. 2009;32:312-317.
27. Maass SWMC, Brandenbarg D, Boerman LM, Verhaak PFM, De Bock GH, Berendsen AJ. Fatigue among long-term breast cancer survivors: a controlled cross-sectional study. *Cancers (Basel)*. 2021;13:1-11.
28. Purcell A, Fleming J, Bennett S, Burmeister B, Haines T. Determining the minimal clinically important difference criteria for the multidimensional fatigue inventory in a radiotherapy population. *Support Care Cancer*. 2010;18:307-315.

29. Herle M, Micali N, Abdulkadir M, et al. Identifying typical trajectories in longitudinal data: modelling strategies and interpretations. *Eur J Epidemiol*. 2020;35:205-222.
30. Ram N, Grimm KJK. Growth mixture modeling: a method for identifying differences in longitudinal change among unobserved groups. *Int J Behav Dev*. 2009;33:565-576.
31. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *J Stat Softw*. 2017;78(2):1-56.
32. Biering K, Frydenberg M, Pappot H, Hjollund NH. The long-term course of fatigue following breast cancer diagnosis. *J Patient-Rep Outcomes*. 2020;4:4.
33. Donovan KA, Jacobsen PB, Andrykowski MA, et al. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *J Pain Symptom Manage*. 2004;28:373-380.
34. Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing fatigue and depression in patients with cancer. *Semin Clin Neuropsychiatry*. 2003;8:229-240.
35. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11:597-609.
36. Bower JE, Ganz PA, Irwin MR, et al. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism. *J Clin Oncol*. 2011;29:3517-3522.
37. Xiao C, Miller AH, Felger J, Mister D, Liu T, Torres MA. Depressive symptoms and inflammation are independent risk factors of fatigue in breast cancer survivors. *Psychol Med*. 2017;47:1733-1743.
38. Ho SY, Rohan KJ, Parent J, Tager FA, McKinley PS. A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. *J Pain Symptom Manage*. 2015;49:707-715.
39. Trudel-Fitzgerald C, Savard J, Ivers H. Which symptoms come first? Exploration of temporal relationships between cancer-related symptoms over an 18-month period. *Ann Behav Med*. 2013;45:329-337.
40. Bødtcher H, Bidstrup PE, Andersen I, et al. Fatigue trajectories during the first 8 months after breast cancer diagnosis. *Qual Life Res*. 2015;24:2671-2679.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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