Breast Cancer (BC) related fatigue: A longitudinal investigation of its prevalence, domains and correlates

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Background

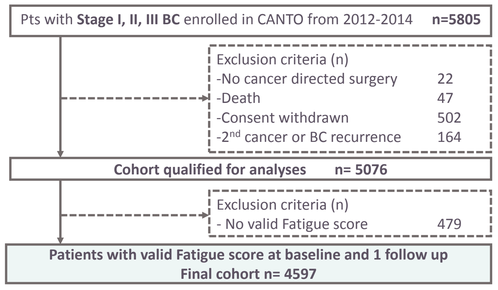
- **Study rationale:** Fatigue is a complex and multidimensional symptom that is recognized as one of the most distressing symptoms in cancer survivorship. During treatment the vast majority of patients experience some fatigue, with up to 60% categorizing their fatigue as severe. Although fatigue typically improves in the year after completion of treatment, a significant portion of patients continue to experience severe fatigue (~30%) in the year after treatment, and limited data suggest that at 10 years post-treatment, 20% of survivors still suffer from severe fatigue[1-3]. Large scale data that help predict and prevent severe fatigue are lacking.
- **Objective:** To characterize longitudinal trajectories of fatigue after breast cancer treatment, and to explore factors associated with varying fatigue trajectories

Patients and Methods

- **Data source:** Prospective longitudinal cohort of patients with early BC treated since 2012 across 26 French cancer centers (CANcer TOxicities [CANTO]; NCT01993498, expected end of accrual of 12,000 pts by end of 2018). For the present analysis, updated information from 5,801 patients was accessed (07/2018 data lock) (**Fig. 1**).
- **Variables of interest. 1.Outcome variables:** Fatigue as per European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ)-C30 ≥ 40 for overall fatigue and EORTC F12 ≥ 40 for physical, emotional and cognitive domains of fatigue[1]. **2.Covariates:** Demographic, clinical, tumor, treatment characteristcs, insomnia and pain as per EORTC-QLQC30, physical activity as per Global Physical Activity Questionnaire [GPAQ]-16, and psychological characteristics including anxiety and depression as per the Hospital Anxiety and Depression Scale [HADS]), optimism and pessimism as per Life orientation test. (**Table 1**).
- **Schedule of longitudinal reassessments:** In this cohort, reassessments occurred at BC diagnosis (baseline) and at T1 (median time post baseline [interquartile range, IQR]: 11 months [8-12]) and T2 (median time post baseline 23 months [20-25]).
- **Statistical analysis:** Multivariate group-based trajectory modeling (GBTM)[4] assessed over time risk of severe Fatigue. Trajectory groups are defined using standard methods, including the Bayesian information criterion (BIC). Multivariate logistic regression examined factors associated with membership to specific risk trajectories.

References: [1]Abrahams , 2016; [2]Bower JE, 2000; [3]Bower JE, 2014 [4]Nagin DS, 2005 and 2010.

Fig. 1



Results

- **1) Trajectory groups of risk of Fatigue:** According to GBTM, pts cluster in distinct trajectory groups relative to their risk of reporting severe Fatigue. **Two main clusters** were identified for overall Fatigue and for each dimension: **one following a high risk trajectory** (dark shade), and **one following a low risk trajectory** (light shade).
- All Trajectories represented below are adjusted by **time fixed variables** (age, menopausal status, marital status, education, income, stage, comorbidities, BMI, receipt of chemotherapy, hormonotherapy, trastuzumab, radiation, breast and axillary surgery, optimism and pessimism) and **by time-dependent variables** (depression, anxiety, insomnia, pain, vasomotor symptoms, BMI and physical activity).
- Trajectories are depicted in Fig. 2A-D: Continuous lines represent estimated trajectories and dotted lines their respective 95% confidence limits. % pts belonging to each group are reported in each legend. **Boxes under the graph include time-dependent variables that were associated (p<.05) with the trajectory shape** (following the respective color scheme).
- **Baseline Characteristics associated with trajectory group:** Detailed information on the distribution of pts *baseline characteristics* by trajectory group are showed in **Table 1**. For each characteristic, we also report Odds Ratios (OR) and 95% CI favoring membership to the high risk group.

Fig 2. GBTM analysis. Latent group-trajectories of risk of severe **overall Fatigue** (2A) and of its **three dimensions**, Emotional (2B), Physical (2C) and Cognitive (2D) are explored. Y axis reports % of risk over time. **Boxes under the graph include time-dependent variables that were associated (p<.05) with the trajectory shape** (following the respective color scheme).

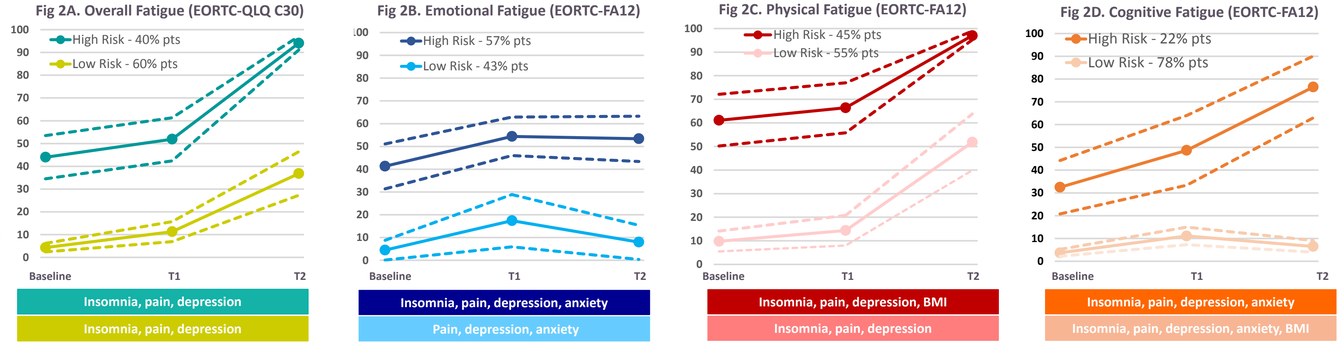
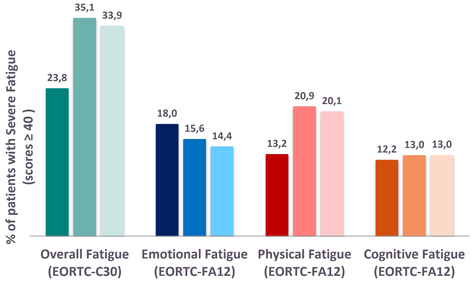


Table 1. Baseline characteristics multivariate logistic regression for trajectory membership

Baseline characteristics	Overall Fatigue (EORTC-QLQ C30)			Emotional Fatigue (EORTC-FA12)			Physical Fatigue (EORTC-FA12)			Cognitive Fatigue (EORTC-FA12)		
	Low Risk 60% pts	High Risk 40% pts	OR of membership to High risk	Low Risk 43% pts	High Risk 57% pts	OR of membership to High risk	Low Risk 55% pts	High Risk 45% pts	OR of membership to High risk	Low Risk 78% pts	High Risk 22% pts	OR of membership to High risk
Age* (years)	58 (49-66)	53 (45-61)	**0.97 (0.95-0.98)**	57 (48-65)	53 (46-63)	0.99 (0.97-1.00)	57 (48-65)	54 (46-63)	**0.97 (0.97-0.99)**	57 (48-65)	52 (45-59)	0.98(0.96-1.00)
<3000€/month** vs ≥	12.09%	18.83%	**1.35 (1.03-1.77)**	12.93%	19.13%	**1.43 (1.05-1.94)**	11.78%	19.44%	**1.57 (1.20-2.04)**	13.20%	22.82%	**1.73 (1.18-2.52)**
Charlson ≥1 (vs. 0)	18.98%	22.75%	**1.30 (1.05-1.60)**	19.20%	23.97%	1.26 (0.99-1.60)	18.21%	24.49%	**1.44 (1.17-1.76)**	19.97%	21.46%	0.99 (0.71-1.37)
Smoker (vs. not)	13.52%	23.51%	**1.51 (1.27-1.80)**	14.71%	24.19%	**1.41 (1.16 -1.73)**	13.62%	23.12%	**1.32 (1.11-1.56)**	15.44%	26.65%	**1.41 (1.08-1.83)**
Stage 1 (vs. 2+)	53.01%	45.59%	0.93 (0.75-1.61)	52.09%	45.52%	0.86 (0.69-1.11)	52.91%	46.08%	0.96 (0.77-1.19)	52.06%	39.33%	0.73 (0.52-1.02)
Radiotherapy (vs. No)	90.94%	91.40%	0.96 (0.69-1.34)	91.06%	91.16%	1.12(0.75-1.67)	90.64%	92.09%	1.27 (0.91-1.79)	90.73%	94.38%	**1.91 (1.09-3.34)**
Chemotherapy (vs. No)	50.67%	59.61%	1.04 (0.83-1.21)	58.05%	52.25%	0.99 (0.77-1.28)	51.35%	57.95%	1.06 (0.85-1.31)	52.43%	62.02%	0.81 (0.58-1.14)
Hormonotherapy (vs. No)	80.98%	82.95%	**1.29 (1.03-1.62)**	81.37%	82.43%	1.04 (0.80-1.35)	81.08%	82.68%	1.17 (0.94-1.46)	81.52%	82.02%	0.97 (0.70-1.37)
BMI ≥25 (vs. < 25)	46.41%	50.00%	**1.27 (1.05-1.49)**	49.00%	53.08%	1.15 (0.93 -1.41)	47.42%	55.15%	**1.41 (1.19-1.69)**	50.33%	49.21%	0.99 (0.75-1.30)
Depressive symptoms*	3 (1-5)	5 (2-8)	**1.10 (1.06-1.13)**	3 (1-5)	7 (4-10)	**1.14 (1.11 -1.18)**	3 (1-5)	6 (3-9)	**1.16(1.13-1.20)**	3 (1-6)	7 (5-10)	**1.14 (1.09-1.19)**
Anxiety symptoms*	8 (5-8)	10 (7-13)	1.00 (0.98-1.03)	8 (5-11)	12 (9-15)	**1.09 (1.05-1.12)**	8 (5-11)	10 (7-13)	1.01 (0.98-1.03)	8 (6-11)	13 (9-16)	**1.12 (1.08-1.16)**
Insomnia*	33 (0-67)	67 (33-100)	**1.01(1.01-1.13)**	33 (0-67)	67 (33-100)	**1.01 (1.00-1.01)**	33 (0-67)	67 (33-100)	**1.01 (1.00-1.01)**	33 (0-67)	67 (33-100)	1.00 (0.99-1.01)
Pain*	0 (0-17)	17 (0-33)	**1.03 (1.03-1.04)**	0 (0-17)	17 (0-33)	**1.02 (1.01-1.02)**	0 (0-17)	17 (0-33)	**1.02 (1.02-1.03)**	0 (0-17)	33 (0-33)	**1.02 (1.01-1.02)**
Hot Flashes (vs. No)	30.76%	36.21%	1.06 (0.89-1.28)	30.96%	38.46%	1.20 (0.98-1.48)	30.22%	37.39%	**1.27 (1.06-1.52)**	31.59%	39.90%	1.29 (0.98-1.70)
Area under the curve			**0.78**			**0.81**			**0.77**			**0.83**

* For each 1-point increase, Adjusted for all listed factors + hormonal status, marital status, education, breast and axillary surgery, physical activity, optimism, pessimism. **Household Income. Significant (p<.05) values are bolded.

- **2) Absolute prevalence of Fatigue:** Overtime prevalence of severe overall Fatigue and of its three dimensions is represented in **Fig.3.** Left bar= baseline; middle bar= T1; right bar= T2.



Conclusions

- **1/3 of patients** report **overall severe Fatigue** after breast cancer diagnosis and treatment.
- The **prevalence overtime differs by Fatigue dimension (emotional, physical and cognitive).**
- The utilization of clustering techniques allowed the identification of patients with a high likelihood of severe Fatigue overtime. **There are clusters of patients with over 90% risk of experience severe Fatigue at almost 2 years after diagnosis.**
- **Psychological distress and symptoms at baseline and overtime impact the development of all fatigue dimensions**, nevertheless we found some heterogeneity in how the trajectories of fatigue evolve across different subgroups of patients.
- **Our data aid in the identification of patients who have increased risk of severe fatigue over time and highlight the need for personalized interventions to ameliorate this burdensome problem.**

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