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## **Determinants of distinct trajectories of fatigue in patients undergoing chemotherapy for a metastatic colorectal cancer: 6-month follow-up using Growth Mixture Modeling**

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## Abstract

**Objective:** This longitudinal prospective and observational study was designed to identify fatigue trajectories during a 6-month period of chemotherapy in patients with metastatic colorectal cancer, and examine the psychosocial factors predicting these trajectories. Associations between fatigue and survival were also investigated.

**Methods:** A total of 169 patients ( $M_{age}=64.36$  years,  $SD=10.5$ ) reported their fatigue levels every 2 weeks for 6 months. Psychological variables (anxiety, depression, internal control, and coping) were assessed at baseline. A Growth Mixture Model was used to identify latent trajectories of fatigue, and a multinomial logistic regression tested covariate predictors of patients' trajectories.

**Results:** Four clinically distinct fatigue trajectories were identified: intense fatigue (6.51%), moderate fatigue (48.52%), no fatigue (33%), and increasing fatigue (11.83%). Fatigue severity was directly associated with overall survival. High depression levels were associated with fatigue severity over time for intense ( $OR=1.80$  [1.32-2.47]) and for moderate ( $OR=1.58$  [1.25-2.00]) fatigue, compared to patients reporting no fatigue. Patients who did not report fatigue were better adjusted, and had more resources, such as better internal control over the disease and less emotion-focused coping (guilt and avoidance), than those who reported intense ( $OR_{control}=0.77$  [0.65-0.92]) or moderate ( $OR_{control}=0.89$  [0.79-0.99] and  $OR_{coping}=1.13$  [1.02-1.24]) fatigue.

**Conclusions:** Fatigue trajectories differed considerably across patients with metastatic colorectal cancer. This first longitudinal study on colorectal cancer patients involving transactional variables suggests that psychosocial interventions should target these specific outcomes, in order to help patients manage their fatigue.

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**Key message:** This article describes a prospective study that describes distinct trajectories of fatigue in metastatic colorectal patients undergoing chemotherapy. It is the first study on this population and the only one considering psychological determinants to explain fatigue intensity during treatment. This research sets the stage for psychosocial interventions to target these issues and manage fatigue.

**Keywords:** cancer, fatigue, trajectories, latent class growth analysis, depression

**Running title:** Determiners of fatigue trajectories during chemotherapy

## Background

Cancer-Related Fatigue (CRF) is almost universal among patients undergoing chemotherapy (1,2). Patients with metastatic colorectal cancer (CRCm) may follow several chemotherapy cycles, and their functional status tend to deteriorate with each in-line treatment (3). CRF prevalence is around 75% in patients with metastatic disease (4,5), as they have undergone months or years of treatment, and experienced a great many side effects (6). A study including patients undergoing palliative treatment reported that CRF predicted a deteriorating QoL to an even greater extent than clinical or demographic factors (7). Fatigue is also an indicator of survivorship. In a recent meta-analysis conducted in 2019 (8), physical functioning and fatigue predicted overall survival more often than other patient-reported outcomes in metastatic disease.

Longitudinal studies allow a deeper understanding of how symptoms change. Miller, Maguire, and Kearney (2007) studied chemotherapy-induced symptoms (nausea, vomiting, oral problems, and fatigue) in 249 patients every day during a 2-week chemotherapy cycle. Fatigue was reported by 57% of patients, and was severe in 15%. Changes in fatigue across the 14 days were represented by a single overall trajectory, reflecting the mean fatigue score for the entire sample. Results showed that fatigue peaked in the first week, and was associated with distress ( $r = .725$ ,  $p = .01$ ) (Miller et al., 2007). Although it can be useful to identify an overall trajectory, it is also important to bear in mind that the same treatment does not necessarily lead to the same patient experience, and it seems relevant to identify distinct trajectories.

Several studies have investigated heterogeneous fatigue trajectories in patients with cancer (10–12). However, they only assessed the development of fatigue after treatment completion, relied on retrospective reports of fatigue, or had a relatively short follow-up period (i.e., 8 months after diagnosis). In the international literature, there is just one study of fatigue trajectories in CRC (13), and this was limited to cancer survivors. Studies investigating the heterogeneity of fatigue trajectories have applied the Latent Class Model to identify distinct fatigue trajectories. In a recent literature review (Baussard & Cousson-Gelie, 2020), we found 16 studies that had used this methodology. Seven (43.75%) focusing on fatigue only, and therefore seems that there is no consensus about the number of trajectories. To our knowledge, no study has yet been conducted to understand fatigue trajectories in patients with CRCm undergoing chemotherapy in relation to psychological variables. Of the

16 above-mentioned studies, three studies (18%) attributed CRF severity to psychological variables, specifically anxiety, depression, and QoL. Two of these identified three CRF trajectories (13,15), whereas Aouizerat et al. (2015) found only two CRF trajectories (16). More specifically, only two of the studies focused on patients with CRC: one among cancer survivors (13), which identified three trajectories, and one among newly diagnosed patients, which identified four trajectories (17).

None of the previous studies was based on a theoretical framework, which may explain the paucity of results for the psychological determinants of fatigue. Personality can impact CRF just as much as it influences QoL, and we can assume that it also has an impact on fatigue over time because of the way that patients deal with it. According to the integrative and multifactorial model in health psychology (18,19), symptoms such as CRF can be explained by psychological antecedents (depression and anxiety), but also by individual resources (i.e., the ways in which patients cope with their symptoms). Some authors have found that anxiety, depression and emotional distress are strongly associated with CRF (10,20–22), even in patients with CRC (23–25). However, too few studies have considered coping and perceived control as resource variables, and these have never been investigated as a key concept in a theoretical framework. Although studies of coping have not yet reached a consensus, emotion-focused coping appears to have detrimental effects (26–28), while problem-focused coping appears to be more beneficial (28–30). Given the need for longitudinal studies and the lack of understanding of fatigue etiology, plus a clinical need for more personalized care, we set out to identify subgroups of patients with CRCm with distinct CRF trajectories during chemotherapy.

We hypothesized that:

- 1) Three distinct fatigue trajectories would adequately describe our population:
  - a. a group with fatigue increasing over time;
  - b. a group with intense fatigue over time;
  - c. and a group with no fatigue at all.
- 2) Psychological variables as identified in our literature review (emotional distress, and patients' resources such as coping strategies and perceived control) would be associated with increasing fatigue over time.
- 3) Finally, each fatigue trajectory is associated with a risk of death. Patients with intense fatigue during treatment may have the lowest survival rate.

## Methods

### Participants

Patients with CRCm who had to start a new chemotherapy protocol were recruited in four hospitals in France. Patients younger than 18 years, those not able to understand French and those with brain metastasis, cognitive impairment, or psychiatric disorder were excluded. The study was briefly introduced during the consultation with the oncologist to plan the new treatment (because of metastasis or failure of previous chemotherapy). As shown in Figure 1, patients' eligibility was checked during this consultation (T0). All participants received an information letter and an informed consent form during the consultation, and had 2 weeks to confirm their participation. If they met the inclusion criteria, and agreed to take part, patients were included in the study before the start of the new treatment (T1). They were included for 6 months (end of follow-up, T4), but met their oncologist every 2 months (T2 and T3) to check treatment effectiveness and tolerance. Patients' data were excluded if their medical treatment changed, or if they decided to withdraw from the study (see Fig. 1). The study was approved by the French Data Protection Authority (CNIL; no. DR-2015-730) and by the Sud-Méditerranée II IRB. This trial was also registered (31) on [isrctn.org](http://isrctn.org) (no. ISRCTN18044948).

### Measures

Demographic and clinical variables were obtained from self-reports at T1 and from medical records. We consider depression, anxiety, internal control, and coping strategies as potential psychological predictors of fatigue. All these variables were assessed via questionnaires at T1, T2, T3 and T4 (see Fig. 1).

#### **Fatigue.**

Fatigue was our primary outcome and had to be assessed with a short tool adapted to repeated measures. Fatigue was assessed every 2 weeks (see Fig. 1), on the day of the chemotherapy treatment, using a standardized visual analog scale, developed and validated among French patients with cancer (32). The Daily Fatigue Cancer Scale (DFCS) consists of three questions measuring physical, emotional and general fatigue at time  $t$ . For each question, patients answered by moving a cursor along a scale ranging from 0 (*Not at all*) to 10 (*Extremely*). In the present study, we only used the results for physical fatigue ("lack of energy") to estimate the latent trajectories (emotional fatigue trajectories will be discussed in other paper).

### ***Depression and Anxiety.***

We used the Hospital Anxiety and Depression Scale (HADS) to measure depressive and anxious symptoms (33). This scale is often used in clinical or oncology research (34). It includes 14 items (seven for each dimension). Items are scored on a 4-point scale ranging from 0 to 3. For both subscales, the maximum score is 21, and a cut-off score  $\geq 8$  indicates a clinical level of anxiety or depression (35).

### ***Perceived control.***

We chose the Cancer Locus of Control Scale to assess perceived control of the illness (36). We used the 14-item French version (37), which has three dimensions: perceived control over the course of the illness (5 items), internal causal attribution (6 items), and religious control (3 items). For each item, patients were requested to indicate agreement on a 4-point scale ranging from 1 (*Not at all in agreement*) to 4 (*Full agreement*).

### ***Coping strategies.***

We considered three distinct coping strategies in this study, using the French version validated among cancer patients (Cousson-Gélie et al., 2010) of the Ways of Coping Checklist (WCC) developed by Lazarus & Folkman (39). Coping strategies are problem-focused strategy, emotion-focused strategy, and social support seeking. Patients indicate their agreement with 21 items on a 4-point Likert-type scale ranging from *No* to *Yes*.

## Statistical Analysis

We used a Growth Mixture Model<sup>1</sup> (GMM) (40,43) to identify subgroups of patients with distinct CRF trajectories. GMM is a data-driven approach used to determine the smallest number of groups or classes of patients that can explain the heterogeneity in outcome changes over time (44). Class-specific CRF trajectories were modelled using a flexible mixed model that accounted for (a) the departure from normality of CRF using a parameterized link function based on quadratic integrated splines with two internal nodes placed at 0.5 and 2 (45), (b) the potential nonlinear trajectory of normalized CRF using a quadratic function of continuous time since inclusion, and (c) the correlation between individual repeated data using individual Gaussian correlated random effects on the functions of time. By relying on the mixed model theory and maximum likelihood estimation, our analyses were robust to missing (intermittent or dropout) data, under the missing-at-random mechanism. Given the high risk of death in this population, we simultaneously modelled the associated risk of death in each latent class with a class-specific Weibull instantaneous hazard.

We estimated GMM models considering between one and five latent classes. For each one, the estimation was repeated using 100 random initial values, to avoid any spurious convergence toward a local maximum. The following criteria were applied to choose the final model. First, we assessed the model's good fit to the data using the sample-size adjusted Bayesian information criterion (SABIC; the lower the better), which has very good performances in retrieving the correct number of classes in mixture problems (46). The quality of the classification yielded by the GMM was assessed by entropy, where values close to one indicated good separation of trajectories and accurate classification of individuals according to these trajectories, and the table of posterior classification (Proust-Lima et al., 2014). Respondents were a posteriori assigned to the class for which they had the highest posterior membership probability. The factors that discriminated between the identified classes were determined using weighted multinomial logistic regression. Differences in the psychological variables (mean scores) between identified CRF classes were determined with *t* tests. All tests were two-sided and significant if  $p < .05$ . Demographic and clinical characteristics were analyzed as descriptors of fatigue trajectories, using mean values for continuous descriptors and frequencies for categorical descriptors, both weighted by the estimated individual trajectory membership probabilities.

GMM analyses were conducted in R (version 3.2.3) using the Jointlcmm function of the lcmm package (47).

## Results

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<sup>1</sup> We chose to rely on a flexible GMM that appropriately handled the skewness in the fatigue visual analog scale (Proust-Lima et al., 2013), the correlation between the repeated measures for each individual, and the association with the risk of death (40), while considering other types of missing data as missing at random (41). In addition, we followed the GRoLTS checklist for reporting latent trajectory studies (42).

## Sample Characteristics

Of the 203 eligible patients screened by oncologists, 169 signed the informed consent form (84%). As described in Figure 1, among those who did not sign, 19 declined, 14 did not meet the inclusion criteria, and one died before inclusion. Among the 169 patients included at T0, 115 were followed at 2 months (T2), 63 at 4 months (T3) and 48 completed the full 6-month follow-up (T4). The longitudinal design and metastatic population can explain the attrition. Among the 121 patients lost to follow-up, 32.2% ( $n = 39$ ) were dropped because their treatment changed after 2 months, 37.2% ( $n = 45$ ) after 4 months and 11.6% ( $n = 14$ ) before the end of the study. Also, 11 (9.1%) withdrew their consent. Finally, 11 (9.1%) died during the follow-up period, plus 9 in the next few months ( $n = 22$ ).

Overall sample characteristics are provided in Table 1. The 169 patients had a mean age of 64.36 years (range = 36–90) and were mostly male (58.6%). The majority had a partner (75.7%), 51.5% had a low educational level, and 85.8% were unemployed (retired or for medical reasons). The majority had received their diagnosis within the previous 2 years (71.7%), and were diagnosed with a colon carcinoma (53.8%). Most had Stage III cancer (69.3%), and metastases were located in the liver (39.6%), lungs (11.8%), or both liver and lungs (17.2%).

## Hypothesis 1 : Identifying Fatigue Trajectories

Four distinct fatigue trajectories were identified according to SABIC and entropy measures (Table 2). The 4-class GMM had both the lowest SABIC, indicating the best fit to the data, and the highest entropy (.75), indicating the most discriminating latent class structure. Patients were a posteriori assigned to Classes 1, 2, 3 or 4 with very high probabilities (mean probabilities: .88, .86, .89 and .76).

The first trajectory, shown in black (Fig. 2a), was characterized by high fatigue scores (7/10; 95% CI [5.25, 8.09]) at baseline that increased over time (Wald test = 319.41;  $p < .001$ ). The cut-off to define physical fatigue is 5.5/10 (Baussard et al., 2017). This *intense fatigue* class was the smallest ( $n = 11$ , 6.51%). Patients exhibiting the red trajectory (Fig. 2a) reported *moderate fatigue* over time (3.57/10; 95% CI [3.09, 4.18]). This trajectory was nonlinear, characterized by an initial increase in fatigue, followed by a decrease (Wald test = 108.56;  $p > .001$ ). This second class was the largest ( $n = 82$ , 48.52%). The blue trajectory (see Fig. 2a) was clinically interesting because it was defined by mild or no fatigue at baseline (0.97/10; 95% CI [.63, 1.88]), but which increased over time (Wald test = 99.45;  $p < .001$ ). This *increasing fatigue* class contained 11.83% of our sample ( $n = 20$ ). Patients exhibiting the fourth and last trajectory, shown in green (Fig. 2a), did not complain about fatigue either at baseline (1.76/10; 95% CI [1, 2;01]) or over time (Wald test = 55.39,  $p > .05$ ). This *no fatigue* trajectory represented a third of our sample.

## Hypothesis 2 and 3: Predicting Fatigue Trajectory Groups and Survival

The demographic and clinical characteristics for the total sample and each of the four fatigue trajectories are set out in Table 2. Trajectories did not differ significantly on any of the sociodemographic or medical variables (all  $p > .10$ ), but the occurrence of a death during follow-up was significantly related to fatigue intensity ( $p < .001$ ), as we observed more deaths among patients belonging to the intense fatigue group (72.7%). This result is illustrated in Figure 2b, which shows that patients with the intense fatigue trajectory had a poor survival rate (median survival = approx. 2 months) explaining the largest interval confidence shadow after 4 measurements. This association was also found for patients who complained of moderate fatigue, 12.2% of whom died during follow-up. When we looked at patients' survival rate at the end of the present study's follow-up, 29.3% of patients who reported medium fatigue died within 1 year of inclusion.

Descriptive statistics for potential predictors according to latent trajectory group, along with tests for bivariate relations, are set out in Table 2. Patients in both the intense and moderate fatigue groups reported significantly more depressive symptoms at inclusion than patients with no fatigue ( $p < .001$ ), along with low internal control ( $p < .001$ ), and recourse to emotion-focused coping ( $p = .06$ ).

As shown in Table 3, depression, internal control, and emotion-focused coping were predictive of patients' trajectories. More depressive symptoms at inclusion were associated with a higher probability of being assigned to the intense ( $OR = 1.80, p < .001$ ) or moderate ( $OR = 1.58, p < .001$ ) fatigue group than to the no fatigue group. Greater use of emotion-focused coping at inclusion was associated with a higher probability of belonging to the moderate fatigue group ( $OR = 1.13, p < .01$ ) than to the no fatigue group. Finally, less internal control over the disease was associated with a higher probability of belonging to the intense ( $OR = 0.77, p < .01$ ) or moderate ( $OR = 0.89, p < .03$ ) fatigue group than to the no fatigue group.

## Discussion

The present study examined the fatigue trajectories of patients undergoing chemotherapy for CRCm. We identified four distinct trajectories, representing four different patterns of fatigue over time, instead of the three patterns we had expected to observe (hypothesis 1). A small group of patients (6.51%) reported intense fatigue over the study period (6-month follow-up), half the sample (48.52%) reported moderate fatigue over this period, and a third of the sample (33.14%) had no fatigue. The fourth trajectory was characterized by patients whose fatigue increased over time (11.83%). Hypotheses 1.a, 1.b and 1.c were confirmed.

The unexpected trajectory was the *moderate fatigue* group with the majority of the sample. This is consistent with Müller et al.'s study, which identified four fatigue trajectories, with a moderate fatigue group including 56% of the sample (17). Even though an increasing fatigue trajectory had not described in

the literature (to our knowledge), we expected to observe it in our sample because we focused on patients with a metastatic disease, meaning that they had undergone several previous treatments, which are liable to be associated with greater fatigue (3).

Psychological factors emerged as the strongest predictors of membership of one of these groups (**hypothesis 2**), particularly depressive symptoms, internal control, and emotion-focused coping, which discriminated the intense and moderate fatigue groups from the no fatigue group in bivariate and multivariate analyses. Fatigue and depression are closely related, especially in the context of cancer (48), and this result was consistent with previous studies revealing that depression explains fatigue trajectories (20,23–25).

One major strength of our study was that it was based on a theoretical framework (18,19), and explored several potential psychosocial determinants to understand changes in fatigue over time. In addition to emotional distress, we considered coping strategies and perceived control (i.e., patients' resources) as possible explanations for fatigue severity. To our knowledge, this had never been done before. Our results showed that resilient patients (who did not report fatigue over time) were those who scored the highest on the internal control dimension. By contrast, tired patients (with intense or moderate fatigue trajectories) reported significantly less control than resilient patients. This supports the idea that when the disease is reported as being *totally out of control* (49), patients are more likely to be fatigued. Our results therefore suggest that having good internal control over disease progression has a protective effect on the fatigue trajectory. Research has shown that perceived control has a positive impact on patients' QoL (50,51) and may reduce the emotional distress associated with the disease (52,53). Accordingly, if we consider that fatigue and distress are closely linked in patients who have cancer, our results suggest that internal control has a protective effect on fatigue symptoms.

Our last psychological predictor of fatigue trajectory was recourse to an emotion-focused coping strategy. To assess coping strategies, we administered the WCC, whose items do not consider emotion-focused strategies to involve positive reinterpretations of events. On the contrary, they assess negative feelings linked to the situation (e.g., how the patient "feels bad" (Item 6), "feels guilty" (Item 9), "if he criticized himself"(Item 20), or "tried to forget everything "(Item 16)). These items clearly imply that the patients' way of handling a situation is not the most suitable way, even in their own eyes. In this sense, our results confirmed that emotion-focused coping has negative effects on fatigue and its changes over time, as suggested by other authors (26–28).

Beyond the fatigue predictors, the present study allowed us to highlight a link between fatigue intensity and survival (hypothesis 3). Our results indicated that 72.7% of patients reporting intense fatigue" died during follow-up. After controlling for medical variables such as years since diagnosis or number of treatments, these patients did not differ significantly from other patients with other trajectories, further

emphasizing the link between fatigue and survival. Efficace et al. (54) demonstrated a clear relationship between social functioning and survival, and concluded that their findings argued in favor of investigating underlying biological mechanisms, as well as collecting patient-reported health-related QoL data in routine clinical practice, as these could provide valuable prognostic information.

### **Study limitations**

The present study had several limitations. First, we had no data for individuals who refused to take part, and could therefore not estimate the impact of selection bias. Second, our sample sizes for the individual fatigue trajectories were small (11-82), resulting in limited power to detect baseline factors that differentiated between the trajectories. Treatment and medical or sociodemographic factors might have emerged as significant predictors in a larger sample. Patients treated for metastatic cancer do not all have the same background. In our sample, some patients had been diagnosed more than 10 years earlier, and had therefore been undergoing treatment for a very long time before entering the study. Others had just been diagnosed with metastatic cancer, and the chemotherapy they underwent during the study was their first round. Others again had experienced a period of remission followed by a recurrence, leading them to resume chemotherapy. Even though these different conditions were considered as controlled variables, a larger sample might have allowed us to attribute fatigue intensity to the depression induced by the duration of the illness or anxiety triggered by recurrence. Third, we did not assess risk factors such as physical activity, fatigue catastrophizing or sleep problems, which may also play an important role in persistent fatigue (10,23,55,56). Finally, as common in longitudinal studies and especially when considering a metastatic disease, our sample suffered from high attrition. As shown in Figure 1, almost 58% of our sample changed treatment during the follow-up and therefore left the study. Our statistical analyses included patients information until they changed treatment and drop out. In addition, as relying on the maximum likelihood approach, (see note above, p.8), our results are robust under the assumption of Missing at Random (MAR) mechanism which stipulates that dropout may be linked to the observed fatigue information. However, to further explore attrition, we compared in each latent class (see “supplementary material”) the fatigue and psychological variables scores among those who changed treatment and dropped out with those who continue the chemotherapy. These additional results indicate that fatigue predictors, such as emotional distress or coping strategies, are also indices that can provide information on treatment compliance: patients who change treatment (drop out of the study) were more anxious during the measurement that preceded their exit, and used few functional strategies, which reflects a poor psychological adjustment during treatment.

### **Clinical implications**

The findings of this study may have implications for clinical practice. Highlighting substantial individual variability in response to cancer treatment and identifying distinct groups of patients with different experiences of fatigue will facilitate the development of targeted interventions for those most at risk. Similarly, the psychological determinants we identified could be used to help screen and provide early interventions for vulnerable patients, in order to reduce fatigue and its consequences on the QoL of patients with cancer.

To reduce fatigue, the National Cancer Comprehensive Network (NCCN) emphasizes several types of interventions such as patient education, physical activity and psychosocial interventions. Psychosocial interventions include Cognitive Behavioral Therapies (CBT). CBTs for cancer patients typically include control of stressful situations (announcement, surgery, heavy treatments or medical examinations) and problem solving, but also a range of other approaches that consider that cognition can be relearned, in turn facilitating behavior change (57–60). The effectiveness of CBT in the management of cancer-related symptoms, including sleep problems and fatigue, has been demonstrated by several authors (57,60–62). However, these interventions focus on fatigue itself, and not on the psychosocial determinants of this fatigue revealed by our study. The determinants of fatigue can be addressed by CBT, in particular by working on the thoughts and cognitive distortions associated with the symptom of fatigue. The goal is to modify the patient's representations and to help him/her tame this symptom (gain control and choose effective coping strategies) through psycho-educational work.

## **Conclusion**

Investigating symptom burden beyond mean trends can enable clinicians to identify those patients most in need of treatment. A same localization or treatment does not necessarily result in the same outcomes. This first longitudinal study involving transactional variables suggests that psychosocial interventions focusing on emotion regulation or dysfunctional thought may help patients and clinicians in the development of an integrative approach.

## **Conflict of interest statement**

There are no financial disclosures or conflicts of interest to disclose.

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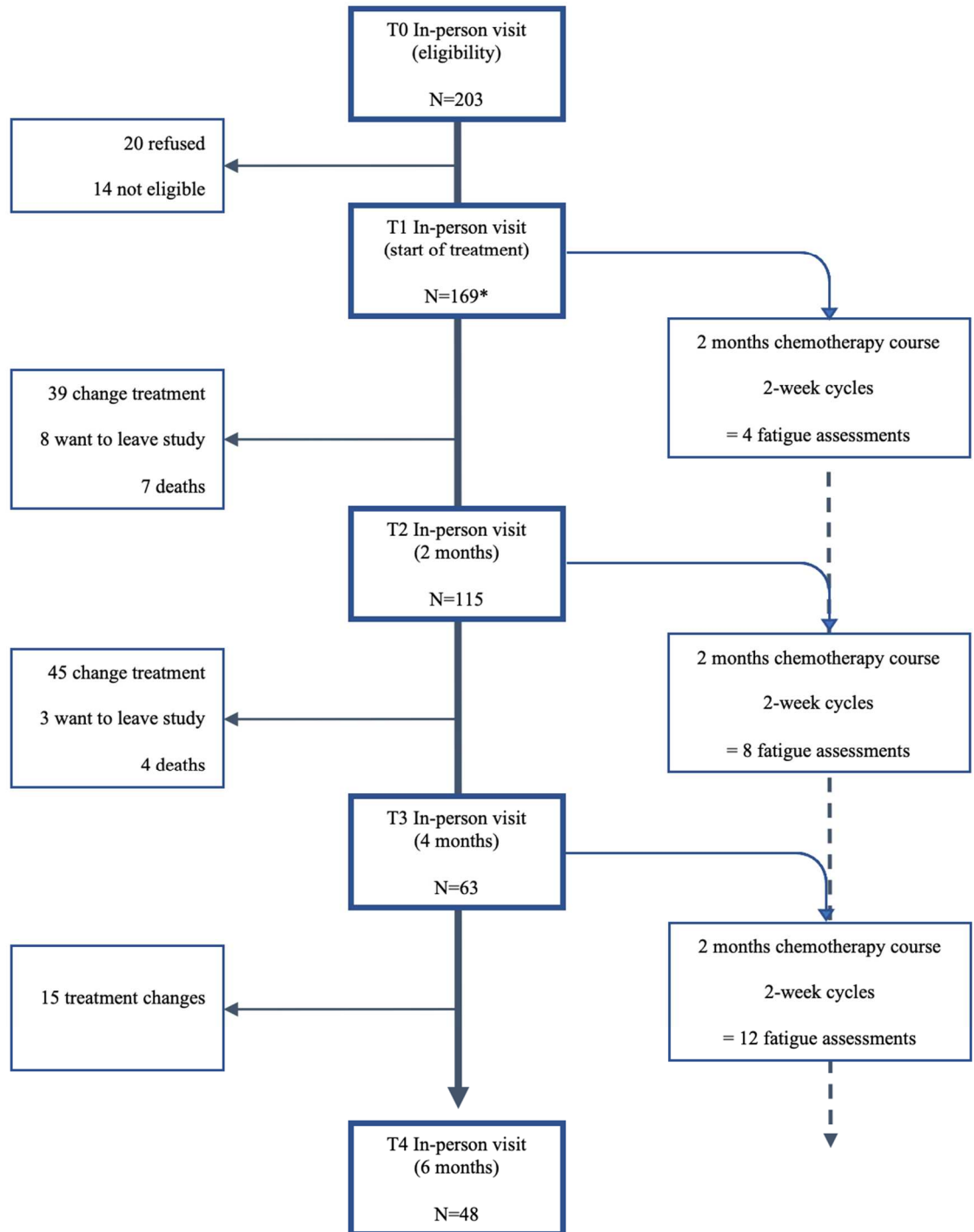


Figure 1. Flowchart indicating the number of patients who completed each assessment. \*Note that 169 patients were considered for the GMM.

Table 1

## Patient Characteristics for the Whole Sample and for Each Cancer-Related Fatigue Trajectory

	Latent Trajectory Group					p value
	Overall (N = 169)	Intense fatigue (n = 11)	Medium fatigue (n = 82)	No fatigue (n = 56)	Increasing fatigue (n = 20)	
<b>Demographic characteristics</b>						
- Mean age (SD) in years	64.36 (10.5)	63.64 (13.21)	63.88 (10.83)	63.93 (9.92)	67.95 (9.00)	.524
- No. men (%)	99 (58.6%)	5 (45.5%)	44 (53.7%)	38 (67.9%)	12 (60%)	.307
- No. in relationship (%)	128 (75.7%)	10 (90.9%)	58 (70.7%)	43 (76.8%)	17 (85%)	.636
- Education						
Less than college degree	87 (51.5%)	5 (45.5%)	44 (53.7%)	23 (41.1%)	15 (75%)	.435
College degree	25 (14.8%)	2 (18.2%)	9 (11%)	12 (21.4%)	2 (10%)	
More than college degree	57 (33.7%)	4 (36.4%)	29 (35.4%)	21 (37.5%)	3 (15%)	
<b>Clinical characteristics (%)</b>						
- BMI						.517
Underweight (< 18.5)	3 (1.8%)	3 (%)	-	-	-	
Normal range (18.5-25)	84 (49.7%)	6 (%)	71 (%)	5 (%)	2 (%)	
Overweight (25-30)	60 (35.5%)	2 (%)	10 (%)	35 (%)	13 (%)	
Obese (> 30)	22 (13%)	-	1 (%)	16 (%)	5 (%)	
- Cancer site						.421
Colon	91 (53.8%)	9 (81.8%)	38 (46.3%)	31 (55.4%)	13 (65%)	
Rectum	55 (32.5%)	-	28 (34.1%)	22 (39.2%)	5 (25%)	
Not defined	23 (13.7%)	2 (18.2%)	16 (19.6%)	3 (5.4%)	2 (10%)	
- Cancer stage at diagnosis						.246
unknown	18 (10.7%)	-	-	-	-	
I	8 (4.7%)	-	3 (3.7%)	2 (3.6%)	3 (15%)	
II	26 (15.4%)	2 (18.2%)	15 (18.3%)	8 (14.3%)	1 (5%)	
III or more	88 (52.07%)	6 (54.5%)	38 (46.3%)	34 (60.7%)	10 (50%)	
- Years since diagnosis						
< 2 yrs	115 (68.05%)	10 (90.9%)	52 (63.4%)	38 (67.9%)	15 (75%)	
> 2yrs & < 5 yrs	34 (20.12%)	-	26 (31.7%)	11 (19.6%)	5 (25%)	
> 5 yrs	20 (11.83%)	2 (18.2%)	7 (8.5%)	9 (16.1%)	2 (10%)	

	Latent Trajectory Group					<i>p</i> value
	Overall (N = 169)	Intense fatigue (n = 11)	Medium fatigue (n = 82)	No fatigue (n = 56)	Increasing fatigue (n = 20)	
- Location of metastasis						.113
Liver	67 (39.6%)	2 (18.2%)	34 (41.4%)	24 (42.9%)	7 (35%)	
Lung	20 (11.8%)	-	8 (9.8%)	8 (14.3%)	4 (20%)	
Both liver & lung	29 (17.2%)	2 (18.2%)	11 (13.4%)	11 (19.6%)	5 (25%)	
Other	53 (31.4%)	7 (63.6%)	29 (35.4%)	13 (23.2%)	4 (20%)	
- Previous treatment (before study)						.172
Chemotherapy (more than 12 cycles? Courses?)	63 (37.2%)	5 (45.4%)	34 (41.5%)	18 (32.1%)	6 (30%)	
Surgery	112 (66.3%)	8 (72.7%)	61 (74.4%)	32 (57.1%)	11 (55%)	
Radiotherapy	38 (22.5%)	3 (27.3%)	22 (26.8%)	11 (19.6%)	2 (10%)	.247
- Treatment line (at T1)	71 (42%)	4 (36.4%)	31 (37.8%)	24 (42.9%)	12 (60%)	
1 <sup>st</sup> line chemo	39 (23%)	2 (18.2%)	20 (24.4%)	16 (28.6%)	1 (5%)	
2 <sup>nd</sup> line chemo	59 (34.9%)	5 (45.4%)	31 (37.8%)	16 (28.6%)	7 (35%)	
3 <sup>rd</sup> line chemo						.972
- Tobacco use	70 (41.4%)	6 (54.5%)	32 (39%)	23 (41.1%)	9 (45%)	
No	74 (43.8%)	4 (36.4%)	38 (46.3%)	24 (42.9%)	8 (40%)	
Stopped	25 (14.8%)	1 (9.1%)	12 (14.7%)	9 (16.1%)	3 (15%)	
Active						<.001
- Death	22 (13%)	8 (72.7%) <sup>abcd</sup>	10 (12.2%) <sup>b</sup>	2 (3.6%) <sup>c</sup>	2 (10%) <sup>d</sup>	
<b>Study variables</b>						
- HADS						
Depression	4.04 (3.13)	8.30 (5.48) <sup>ab</sup>	5.12 (2.69) <sup>c</sup>	2.31 (2.62) <sup>ac</sup>	3.55 (3.38) <sup>b</sup>	<.001
Anxiety	6.55 (3.65)	7.60 (3.81)	7.55 (4.02)	6.56 (3.59)	6.05 (3.03)	.360
- CLCS						
Internal control	19.08 (3.99)	16.00 (4.97) <sup>ab</sup>	18.72 (4.32) <sup>c</sup>	20.13 (3.65) <sup>ac</sup>	19.95 (3.10) <sup>b</sup>	<.001
Causal attribution	8.89 (3.46)	8.33 (3.64)	9.25 (3.65)	8.74 (2.87)	7.35 (3.62)	.402
Religious control	4.61 (2.48)	3.44 (1.33)	4.73 (2.69)	4.45 (2.31)	4.55 (2.46)	.944
- WCC-21						
Problem-focused	19.83 (7.32)	18.00 (7.23)	20.10 (6.89)	20.44 (7.80)	19.50 (5.41)	.187
Emotion-focused	12.15 (5.07)	12.55 (5.79)	13.31 (5.48) <sup>a</sup>	10.91 (5.18) <sup>a</sup>	12.60 (4.81)	.062
Social support seeking	14.47 (6.01)	12.55 (5.48)	14.90 (5.37)	14.30 (6.44)	16.60 (3.93)	.347

*Note.* Values represent means (standard deviation) for continuous variables and frequency (percentage) for categorical variables. *p* values refer to a test for bivariate relations between each variable and trajectory group. Pairwise comparisons were conducted for predictors that showed a significant overall effect. Groups that differed significantly are indicated by the same letter. HADS = Hospital Anxiety and Depression Scale; CLCS = Cancer Locus of Control Scale; WCC-21 = Ways of Coping Checklist.

Table 2

*Comparison of Growth Mixture Models for Different Numbers of Latent Classes*

Model Number of Classes	LL	SABIC	Entropy	% patients in each class*				
				1	2	3	4	5
<b>1</b>	-1915.44	3862.30	-	100				
<b>2</b>	-1899.59	3842.39	.73	65.09	34.01			
<b>3</b>	-1886.14	3827.26	.69	49.70	34.91	15.38		
<b>4</b>	<b>-1874.78</b>	<b>3816.33</b>	<b>.75</b>	<b>6.51</b>	<b>48.52</b>	<b>33.14</b>	<b>11.83</b>	
<b>5</b>	-1871.02	3820.58	.72	7.10	45.56	11.83	20.71	14.79

Note. LL = log-likelihood; SABIC = sample size-adjusted Bayesian information criterion. Selected model shown in bold.

\* According to the highest posterior class-membership probability.

Table 3

*Odds Ratios Comparing Predictors Across Classes*

	Intense fatigue vs. No fatigue			Moderate fatigue vs. No fatigue			Increasing fatigue vs. No fatigue		
	Beta	OR [95% CI]	<i>p</i>	Beta	OR [95% CI]	<i>p</i>	Beta	OR [95% CI]	<i>p</i>
<b>HADS - depression</b>	.59	1.80 [1.32, 2.47]	<.001	.46	1.58 [1.25, 2.00]	<.001	.06	1.06 [0.75, 1.51]	.75
<b>WCC – emotional coping</b>	.10	1.10 [0.93, 1.32]	.27	.12	1.13 [1.02, 1.24]	<.01	.04	1.04 [0.25, 4.27]	.55
<b>CLCS – internal control</b>	-.26	0.77 [0.65, 0.92]	<.01	-.12	0.89 [0.79, 0.99]	.03	-.04	0.96 [0.80, 1.15]	.61

Note. The no fatigue group served as the reference class.

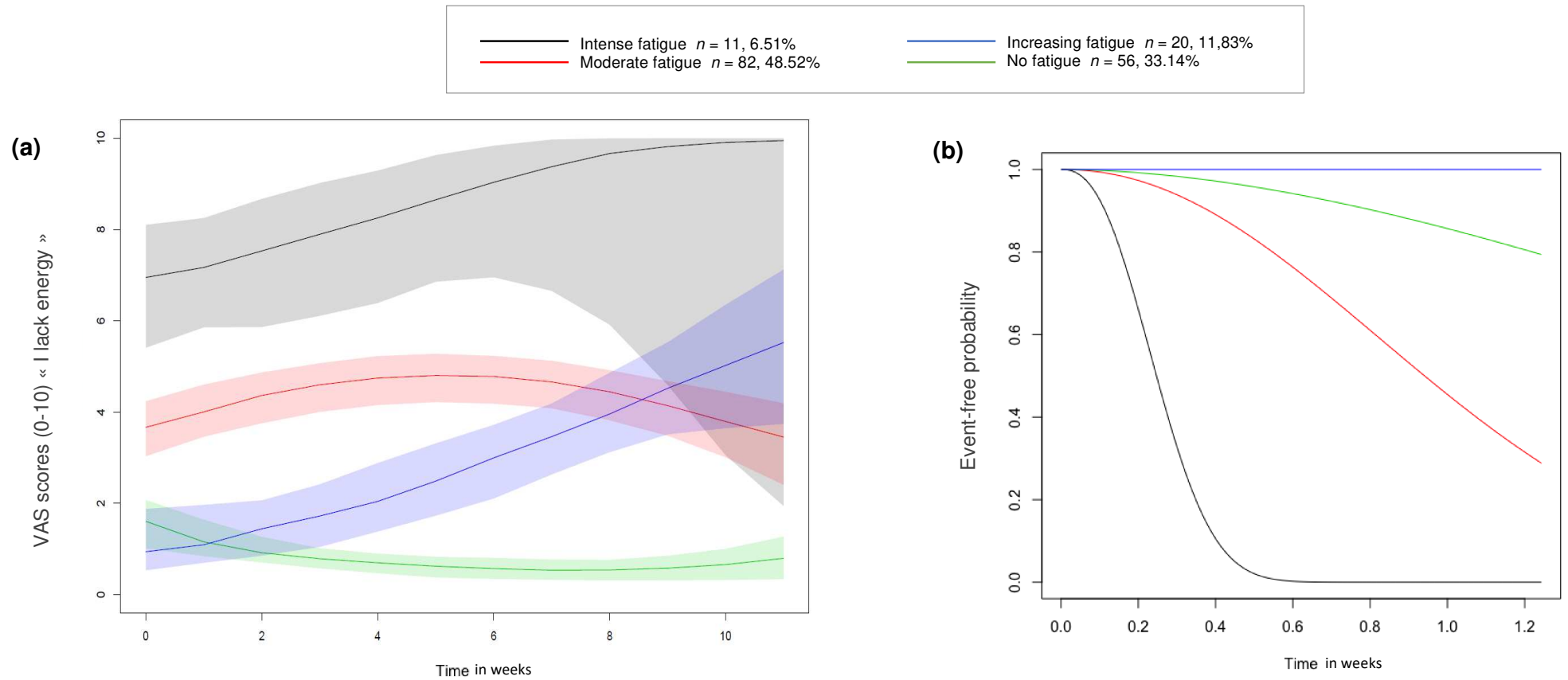


Figure 2: (a) Mean predicted trajectory of fatigue (along with 95% confidence interval in shades) and (b) mean predicted survival probability in the 4 groups over the follow-up period.