



HAL
open science

Neuromuscular, Psychological, and Sleep Predictors of Cancer-Related Fatigue in Cancer Patients

Martin Chartogne, Abderrahmane Rahmani, Sébastien Landry, Hugues Bourgeois, Nicolas Peyrot, Baptiste Morel

► **To cite this version:**

Martin Chartogne, Abderrahmane Rahmani, Sébastien Landry, Hugues Bourgeois, Nicolas Peyrot, et al.. Neuromuscular, Psychological, and Sleep Predictors of Cancer-Related Fatigue in Cancer Patients. *Clinical Breast Cancer*, 2021, 21 (5), pp.425-432. 10.1016/j.clbc.2020.12.002 . hal-04083806

HAL Id: hal-04083806

<https://hal.science/hal-04083806>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Neuromuscular, psychological and sleep predictors of cancer-related fatigue in cancer patients

Martin Chartogne^a, Abderrahmane Rahmani^a, Sébastien Landry^b, Hugues Bourgeois^b, Nicolas Peyrot^a and Baptiste Morel^c.

^a Le Mans Université, Nantes Université, Movement - Interactions - Performance, MIP, EA 4334, F-72000 Le Mans, France.

^b Elsan, Clinique Victor Hugo, Centre Jean Bernard, Le Mans, France.

^c Univ. Savoie Mont Blanc, Laboratoire Interuniversitaire de Biologie de la Motricité, EA 7424, F-73000 Chambéry, France.

Corresponding author

Martin Chartogne - martin.chartogne@univ-lemans.fr

Laboratoire Motricité, Interactions, Performance

Département STAPS – Le Mans Université

Avenue Olivier Messiaen

72000 LE MANS - France

Declarations of interest

None.

Abstract

Introduction/Background - Cancer-related fatigue (CRF) is the most reported side-effect of cancer and its treatments. This distressing sense of exhaustion critically impairs quality of life and can persist for years after treatment completion. Mechanisms of CRF are multidimensional (e.g., physical, psychological or behavioral), suggesting the need for a complex assessment. Nevertheless, CRF remains assessed mainly with one-dimensional questionnaires. The purpose of this study was to test whether neuromuscular parameters enhance a model including well-known predictors of CRF.

Materials and Methods – Forty five participants with cancer history completed self-assessment questionnaires about quality of life, CRF, sleep disturbances and emotional symptoms. They also completed a 5-min handgrip fatiguing test composed of 60 Maximal Voluntary Contractions (MVC) to assess neuromuscular fatigability. Hierarchical linear regression analyses were performed to determine whether the neuromuscular fatigability threshold improved the FA12 score prediction beyond that provided by anxiety-depression and sleep disturbances.

Results - The hierarchical linear regression analysis evidenced that a model including anxiety-depression, sleep disturbances and neuromuscular fatigability explained 56% of CRF variance. Besides, the results suggest that the mechanisms leading to CRF may be different from one person to another.

Conclusion - Results reveal that sleep disturbances, emotional symptoms and neuromuscular fatigability were the most important CRF predictors in cancer patients. This information could be useful for health care professionals offering tailored, individual support to patients with CRF.

Keywords

Cancer-related fatigue; cancer; neuromuscular fatigability; multidimensional; fatigue model; supportive care

Introduction

Cancer patients are especially prone to several side-effects during or after treatment which impairs their engagement in activities of daily living. Cancer-related fatigue (CRF), defined as ‘a distressing persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity that interferes with usual functioning’,¹ is the most frequently reported symptom among these side-effects.² CRF prevalence is up to 50% for cancer patients with 30% reporting CRF two years after treatment and 20% after 5 years.³ This widespread symptom and its negative impact on patient quality of life makes its management essential for providing effective care.

Being that CRF is a subjective symptom, the standard assessment method is to use one of the approximately 40 questionnaires that have been validated (e.g., EORTC QLQ-FA12, FACT-F, BFI).⁴ These surveys evaluate fatigue intensity differently, for instance by considering it either global or multidimensional (e.g., physical, emotional, cognitive). Some of them were also associated with threshold for clinical importance, which enables for the identification of patients requiring further attention by health care professionals.⁵ However, it is acknowledged that CRF mechanisms are likely to be specific to the individual and unlikely to be due to a single or homogenous biological or psychosocial explanation. Considering that the above-mentioned CRF assessments do not allow appreciating the underlying mechanisms involved, it makes difficult to target optimal individual intervention.

Indeed, CRF can be influenced by a variety of demographic, physiological, medical, psychosocial, behavioral and biological factors.⁶ The three most commonly reported are sleep disturbances, anxiety and depression. Several studies have established positive correlations between sleep disturbances and CRF during treatments⁷ and after their completion.⁸ Savard and Morin⁹ concluded that suffering from insomnia adds an additional risk for experiencing

intense and persistent fatigue after cancer treatment. Likewise, the association between anxiety and depression symptoms and fatigue has been established for cancer patients.^{10,11,12}

CRF might also be related to neuromuscular alterations.^{13,14} Some studies reported early neuromuscular fatigability and difference in origins between healthy people and fatigued cancer patients (i.e., shorter endurance time and a greater contribution of central fatigue in exercise limitation).¹⁵⁻¹⁷ In this sense, Twomey et al.¹⁸ proposed a framework to conceptualize the potential link between acute neuromuscular fatigability and CRF. Despite being a pilot study with a small sample size ($n = 14$), a previous work by our team recently suggested that the force-time relationship asymptote assessed during a maximal and prolonged handgrip test might be correlated to CRF.¹⁹ When repeating maximal contractions the muscle force will first decrease in a linear-like manner but if the exercise is prolonged for long enough the force-time relationship become curvilinear and the force capacity will reach a plateau (mathematically the asymptote) that can be maintained indefinitely. This force plateau is a relevant indicator for two reasons: i) it represents the maximal force decrease and thus fatigability from a neuromuscular point of view and ii) it is an important neuromuscular fatigability threshold in exercise physiology, when exercising at intensities below it, the muscle force capacity remain preserved while above fatigability sets drastically.²⁰

Previous studies have proposed multidimensional models to predict CRF utilizing some of the above-mentioned factors. Using a multiple linear regression, Stone et al.²¹ have designed a model explaining 56% of CRF variance including anxiety-depression (assessed through The Hospital Anxiety and Depression Scale (HADS) total score), dyspnea and pain (assessed with the quality of life questionnaire in cancer, EORTC QLQ-C30, single items) and a disease burden score (specially developed by the authors of this study, but not yet validated). More recently, Lockefer and De Vries²² used depressive symptoms, sleep quality and CRF before diagnosis (or primary surgical treatment) in breast cancer patients to predict

CRF at 24 months. Only CRF before diagnosis was a significant predictor of CRF two years later ($r^2 = 0.33$; $p < 0.001$). Humpel and Iverson²³ also investigated the relationship between sleep disturbances, fatigue and physical activity in patients with breast and prostate cancers. They built a CRF prediction model, including sleep quality and total physical activity (assessed through The Pittsburgh Sleep Quality Index (PSQI) and Godin Leisure-Time Exercise Questionnaire, respectively) resulting in a 46% CRF variance prediction. Nevertheless, they focused solely on the behavioral dimensions of CRF.

The purpose of this study was to i) to replicate Veni et al.'s findings of correlation between handgrip force-time relationship's parameters and cancer-related fatigue with a new and larger sample and ii) to test if the addition of neuromuscular parameters derived from a handgrip test to sleep perturbation and anxiety/depression, i.e., the main known predictors of CRF, will enhance the variance explanation of CRF in a regression model. We hypothesized that Veni et al.'s findings will be replicated and that handgrip force-time asymptote will explain a part of the CRF variance that was not explained by sleep or anxiety/depression.

Material and methods

Participants

Forty five participants with history of cancer (ranging from Stage I to Stage IV) were recruited while treatments (chemotherapy, radiotherapy and/or hormone therapy) were in progress or completed within 2 years before the start of the study (Table 1). Patients were not recruited if the referring oncologist identified any contraindication to physical exercise or comorbidities (e.g., neurological, muscular, skeletal disorders or other conditions that would influence their sensorimotor performances). After an explanation of the experimental protocol and associated risks, written informed consent was obtained from participants and the study was conducted according to the Declaration of Helsinki except for registration in a database. Project approval was obtained for this study from the ethics committee of human research.

Table 1 Anthropometric and clinical characteristics of participants

<i>Gender</i>	Females : 40 Males : 5
<i>Age (years)</i>	57.8 ± 11.2
<i>Height (m)</i>	1.63 ± 0.07
<i>Body mass (kg)</i>	67.8 ± 14.7
<i>Body mass index (kg.m⁻²)</i>	25.3 ± 5.3
<i>FA score (/100)</i>	44.9 ± 23.8
<i>FA12 score (/100)</i>	34.1 ± 21.3
<i>Cancer treatment</i>	Under treatment : 32 Treatment completed : 13
<i>Cancer types</i>	Breast : 33 Lymphoma : 4 Ovary : 2 Lung, Prostate, Endometrium, Myeloma,

Experimental protocol

Participants were asked to complete four self-assessment questionnaires, alone in quiet conditions, about quality of life (EORTC QLQ-C30), CRF (EORTC QLQ-FA12), sleep quality and sleep disturbances (PSQI), and anxiety-depression (HADS). The subsequent instructions were provided: “Please answer all questions yourself by circling the number that best applies to you. The information provided will remain strictly confidential. Take as much time as necessary, there are no “right” or “wrong” answers”. Next, a handgrip fatiguing test was administered by research staff using a custom-made device to measure strength (in Newton) in isometric conditions with a load cell (LSB350, Futek, Irvine, USA). Participants first performed a standardized warm-up of ten 4-s isometric contractions at 50% of their maximal self-perceived grip strength using finger flexors from their dominant hand. This warm-up period allowed participants to familiarize themselves with effort duration, guideline and equipment. Two minutes later, they performed two 4-s isometric Maximal Voluntary Contractions (MVC) with 1-minute of recovery in between. If the difference between these MVCs was greater than 5%, a third one was performed. The highest peak force recorded was considered as the MVC in non-fatiguing conditions (F_{\max}) and expressed relatively to body mass. Next, the 5-min fatiguing test was performed composing of 60 4-s MVC, each separated by a 1-s rest. Maximal force (F_{peak}) was recorded during each 4-s MVC set and expressed relatively to the pre-fatigue MVC. Duty cycle was ensured using a metronome with visual and sound signals. To avoid pacing strategies, participants were not informed of the time remaining or the number of MVC performed²⁴. Throughout the experiment, participants remained seated with elbow angle at approximately 90°, wrist in neutral position and non-dominant hand resting on leg. Investigators used verbal encouragement for participants to grip as strong as possible during MVC.

Data Analysis

EORTC QLQ-FA12 total scores (FA12 score) were used as it provides a validate measure of the general degree of CRF,²⁵ ranging from 0 to 100, with higher levels indicating greater degree of CRF. EORTC QLQ-FA12 total score was chosen as it is composed of a multidimensional CRF evaluation (physical, emotional, cognitive, social sequelae and interference with daily life) while the 3-item EORTC QLQ-C30 CRF score (FA score) stresses solely the physical aspect.²⁵ While there is no threshold for clinical importance for the FA12 score, a cut-off value of 39 is used for the FA score to identify fatigue symptoms.⁵ Total PSQI scores (from 0 to 21) were computed as the sum of the seven subscales and then used to distinguish poor and good sleepers.²⁶ The presence of collinearity between anxiety and depression was evidence using a correlation analysis ($r = 0.55$), thus a total combined HADS score (i.e., the sum of anxiety and depression scores, from 0 to 42) was used in the regression analysis instead of separate anxiety and depression scores, as proposed previously by other studies.^{21,27}

Non-linear regression techniques were used to fit the kinetics of F_{peak} in function of time for each participant. Fittings were performed using non-linear least-squares procedures with Matlab 2016a (The MathWorks, Natick, MA, USA). An iterative process was used in order to minimize the sum of squared error between the fitted function (Eq. 1) and observed values.

$$F_{peak} = F_A + (100 - F_A) \times e^{\left(\frac{-t}{\tau}\right)} \quad \text{Eq. 1}$$

where F_A is the force-time asymptote expressed in percentage of the MVC force; t the time in seconds; and τ the curvature constant in seconds. To sum up, three neuromuscular parameters were considered for further analysis i) the maximal handgrip strength pre-fatigue (F_{max} in $N.kg^{-1}$), which represents the functional muscle capacity before any exercise related to muscle mass and nervous activation; ii) the force asymptote (F_A), a threshold above which the

neuromuscular fatigability sets drastically and which is related to muscle aerobic capacity. For further analysis, the relative maximal force decrease (i.e., fatigability; $\Delta F_A = 100 - F_A$) was considered; iii) the curvature constant (τ) which indicates the rate of force decrease (95% of the decrease is done when time reached 3 times τ) and is schematically related to anaerobic capacity.

Statistical Analysis

All data were analyzed with JASP (The JASP Team, University of Amsterdam, Netherlands) and expressed as means \pm standard deviations (SD). The normality of the variables of interest (i.e., FA12 score, age, F_{\max} , ΔF_A , τ , PSQI score, HADS score) were tested using Shapiro-Wilk tests. Homogeneity of variance was verified using Levene's test. A linear regression analysis was performed to verify the influence of F_A on FA12 score and the coefficient of correlation (r) was calculated. Correlation coefficient (r) values of 0.00 to 0.19, 0.20 to 0.39, 0.40 to 0.59, 0.60 to 0.79, and greater than 0.79 were classified as 'very weak', 'weak', 'moderate', 'strong' and 'very strong' respectively, as proposed by Evans.²⁸ A hierarchical linear regression analysis was performed to determine whether the neuromuscular parameters improved the FA12 score prediction beyond that provided by anxiety/depression, sleep and age. Based on previous literature, HADS score, PSQI score and age were first entered into the equation, FA12 score being the dependent variable. In a second step, ΔF_A , F_{\max} and τ were entered into the equation in this order based on their likelihood to have an influence on FA12 prediction from a pilot study.¹⁹ The extra sum-of-squares F test was then performed to test the significance of r^2 change. The correlation matrix including all variables of interest was performed. The z-score transformation of residuals allows to identify outliers with a threshold fixed at ± 3 coefficient of determination (r^2) and change in r^2 (Δr^2) between models were calculated. To assess the predictive power of the variables, the beta coefficients (β) and normalized beta coefficients (β^*) were computed. The root mean square error ($RMSE$) of the predictive model (i.e., square root of the differences between observed and predicted CRF values) was calculated to evaluate the accuracy of predicted CRF in comparison with FA12 score. For all tests, the alpha level for statistical significance was set at $p < 0.05$.

Results

Two outliers were removed from the data reducing the number of case to 43. The mean EORTC QLQ-C30 CRF item (FA score) of the participants of this study was 44.9 ± 23.8 (Table 1). Furthermore, 51.1% of the participants of this study reported clinical relevant CRF (i.e., $FA > 39/100$). Mean data \pm SD for each predictor variable used are presented in Table 2. FA12 total score and F_A were significantly correlated in both Veni et al. and the present study ($r = 0.81$ and $r = 0.50$, respectively; Figure 1). The equation regression (mean [confidence interval at 95%]) was $FA12 = -2.31 [-3.43; -1.19] \times F_A + 159 [101; 218]$ for Veni et al. and was $FA12 = -0.82 [-1.29; -0.34] \times F_A + 74 [50; 99]$ in the present study.

Table 2 Predictor variables used in the multiple linear regression analysis

<i>Variables</i>	<i>Mean \pm SD</i>
Age (years)	57.8 ± 11.2
F_{\max} (N.kg⁻¹)	3.0 ± 1.1
ΔF_A (%)	51.6 ± 13.7
τ (s)	87.7 ± 65.9
PSQI score (/21)	8.7 ± 4.5
HADS score (/42)	13.6 ± 6.9

Correlation matrix to identify colinearity is presented in Table 3 (with *Pearson's r* and *p-value*).

Table 3 Correlation matrix for colinearity identification

	HADS score	PSQI score	ΔF_A	Age	F_{\max}	τ
HADS score	<i>Pearson's r</i>	—				

Table 3 Correlation matrix for colinearity identification

		HADS score	PSQI score	ΔF_A	Age	F_{\max}	τ
PSQI score	<i>p-value</i>	—					
	<i>Pearson's r</i>	0.350*	—				
ΔF_A	<i>p-value</i>	0.021	—				
	<i>Pearson's r</i>	0.421**	0.006	—			
Age	<i>p-value</i>	0.005	0.969	—			
	<i>Pearson's r</i>	-0.022	-0.141	-0.143	—		
F_{\max}	<i>p-value</i>	0.888	0.367	0.361	—		
	<i>Pearson's r</i>	-0.024	0.058	0.065	-0.259	—	
τ	<i>p-value</i>	0.877	0.711	0.677	0.093	—	
	<i>Pearson's r</i>	-0.032	0.171	0.301*	-0.030	0.104	—
	<i>p-value</i>	0.839	0.273	0.050	0.847	0.509	—

* $p < .05$, ** $p < .01$, *** $p < .001$

The results of the hierarchical linear regression are summarized in Table 4 and detailed in Table 5 (with changes in *Fischer's F*, r , r^2 and *adjusted r*²). HADS score, PSQI score and age were entered in the *Model 0* (step 1), HADS and PSQI score being finally included in the model as significant predictors of CRF (explained variance of FA12 score: 47%). ΔF_A , F_{\max} and τ were then entered into the *Model 1* with only FA being significant. The latter significantly improved the r^2 by 8% (Model 1 r^2 was 56%%; $F = 6.05 >$ critical F value = 4.08). Predictive power, i.e., beta coefficients (β) and normalized beta coefficients (β^*), are presented in Table 5 for each predictors.

Table 4 Model summary of regression analyses to determine prediction of CRF

Model	r	r^2	<i>Adjusted r</i> ²	<i>RMSE</i>	r^2 Change	<i>F</i> Change	df1	df2	p
0	0.688	0.473	0.447	15.817	0.473	17.958	2	40	< .001
1	0.746	0.557	0.523	14.684	0.084	7.413	1	39	0.010

Note. Null model includes HADS score, PSQI score

Table 5 Results at each step from the regression analysis for CRF prediction

Model	β	SE	β^*	t	p
0 (Intercept)	-0.330	6.514		-0.051	0.960

Table 5 Results at each step from the regression analysis for CRF prediction

Model	β	SE	β^*	t	p
Included variables					
HADS score	1.776	0.387	0.562	4.590	< .001
PSQI score	1.180	0.590	0.245	2.001	0.052
Excluded variables					
Age	-0.125	0.220	-0.067	-0.569	0.573
1 (Intercept)	-24.318	10.686		-2.276	0.028
HADS score	1.288	0.402	0.408	3.207	0.003
PSQI score	1.432	0.555	0.297	2.579	0.014
Included variables					
ΔF_A	0.569	0.209	0.324	2.723	0.010
Excluded variables					
F_{\max}	-0.889	2.240	-0.045	-0.397	0.694
τ	-0.044	0.041	-0.128	-1.053	0.299

Discussion

The main findings are that i) we replicated the results from Veni et al.¹⁹ in the sense that the handgrip isometric force asymptote was significantly correlated to FA12 total score (regression equation not different from Veni et al.) but we found a lower coefficient of correlation in the present study ($r^2 = 0.25$ vs. 0.65); ii) the hierarchical multiple linear regression reveals that the handgrip isometric force asymptote improves the variance explanation of FA12 total score beyond the variance explained by HADS score (anxiety/depression) and PSQI score (sleep disturbances) ($r^2 = 0.47$ vs. 0.56).

A pilot study by our team¹⁹ suggested that the force asymptote obtained during a maximal repeated handgrip contractions is correlated with the CRF severity in a small sample size ($n = 14$). As, F_A was correlated to FA12 total score (Figure 1), the present study succeeds to replicate this results in a new experimental population with a larger sample size ($n = 43$). However, one should note that the correlation was here moderate while it was strong in Veni et al.'s study ($r = 0.50$ vs. 0.81). The correlation has probably been overestimated previously due to the small sample size. We assumed that the present results were more realistic since the CRF is known to be influenced by a host of covariates being not neuromuscular. The present results showed that age was not a significant covariate of CRF severity (partial $r^2 = 0.01$, $p = 0.573$). While older people generally reported more fatigue than younger, the association between age and CRF is not systematically evidenced. This might be due to other demographical factors which also influence the CRF symptom in cancer population such as marital status and income.⁶ As first-stage predictors, HADS (anxiety/depression) and PSQI score (sleep) explained 47% of the FA12 total score (CRF severity) variance ($p < 0.001$, Table 4). This result is in line with previous literature. First, regarding emotional symptoms, anxiety and depression were investigated in cancer patients for many years and were also correlated with CRF severity (dissociated^{29,30} and combined³¹). When dissociated,

observations suggest that these psychological parameters affected CRF at different times. While anxiety seemed to influence CRF levels before treatment, there were no subsequent CRF increases during treatment. Conversely, an increase in depression during treatment was concurrent to sustained or increased CRF.³² Furthermore, anxiety before treatment was a strong predictor of subsequent CRF^{22,30,32} and depressive symptoms in breast cancer patients.³⁰

Second, sleep disturbances were often reported in fatigued cancer patients (from 17% to 70%), extending from the time of diagnosis to survivorship.³³ Indeed, Martin et al.³⁴ investigated objective measures of sleep and reported that onset latency, wake time at night, and sleep efficiency were correlated with CRF severity. Moreover, circadian rhythm dysregulations have been observed in fatigued cancer patients,³⁵ involving a notable decrease in circulating melatonin implicated in sleep regulation.³⁶ These dysregulations were partly explained by the imbalance between sleep opportunities and sleep ability caused by a different break-up and reorganization of spontaneous daily physical activities (daily living, professional, leisure and sports activities) and a change in activity intensity.

Among second-step predictors, only the handgrip isometric force asymptote was included in the model (Table 5). ΔF_A enhances significantly the CRF variance explanation by around 8% compare to anxiety/depression and sleep disturbances alone (Model 1 $r^2 = 0.56$, Table 4). Previous studies have evidenced early neuromuscular fatigability in fatigued cancer patients¹⁵⁻¹⁷ but our study is the first to show that neuromuscular fatigability can explain a part of CRF variance that was unexplained by known covariates such as sleep disturbances and emotional symptoms. The force asymptote seems to be an interesting indicator since Veni et al.¹⁹ reported, in their pilot study, a strong positive correlation between moderate intensity daily living activities (i.e., >2.5 METs) and the handgrip fatigability threshold (i.e., ΔF_A). According to the theoretical framework proposed by Twomey et al.¹⁸, they hypothesized that

patients decreased their activities of daily living in order to avoid exceeding their reduced fatigability threshold, which, in turn, increased their neuromuscular deconditioning involved in CRF. To our knowledge, this is the first study combining emotional, behavioral and neuromuscular parameters in a CRF predictive model.

The model used in the current study might offer the opportunity to understand predominant CRF mechanisms at the individual level. Two participants (e.g., cancer patients number 37 and 38 in Figure 2) had varying degrees of the different symptoms but had the same CRF level (i.e., observed FA12 of 55.6 for both patients with clinically relevant CRF). They presented different influence of anxiety-depression symptoms, sleep disturbances and neuromuscular fatigability on their CRF estimated from the proposed model (i.e., 12%, 33% and 55% respectively for patient 37; and 31%, 22% and 47% for patient 38). The need for tailored interventions in supportive care based on patient characteristics (e.g., age, gender, physical fitness level, physical activity preference) and cancer characteristics (e.g., type, treatments, side effects) has already been highlighted.^{18,37,38} Because the current results suggest that the mechanisms leading to CRF may be different from one person to another, it could be possible to develop an individual screening methodology based on anxiety-depression symptoms, sleep disturbances and neuromuscular fatigability assessment (using HADS and PSQI questionnaires and a fatiguing test, respectively). Indeed, a handgrip test could be relevant in addition to patient-reported outcomes, already proposed in some guidelines for screening, assessment and management of CRF (including sleep disturbances, depression and anxiety),³⁹⁻⁴¹ as it is commonly used in clinical settings (e.g., for assess global strength capacities). Besides, this would enable supportive care professionals to cater their interventions to individual CRF origins in order to optimize fatigue management. However, although the proposed model may offer interesting information as describes above, one should keep in mind that the screening for clinically relevance of symptoms (e.g. fatigue, sleep

disturbance, anxiety/depression) using validated scales and thresholds are necessary before considering treating it. No study investigated how to address a low neuromuscular fatigability threshold in cancer patients. Nevertheless, reduced neuromuscular fatigability have been observed in breast cancer patients after a 10-week strength training protocol⁴² and this was interestingly associated to a decreased self-perceived fatigue. More generally, resistance training may be an effective intervention to consider when trying to deal with high neuromuscular fatigability in cancer patients.

In the current study, our model explains 56% of the CRF variance (Table 4), but still leaves a significant part of the CRF variance to be accounted for by other parameters. Medical factors, for instance, could have an effect on CRF. Outcomes of patients receiving different therapies have been used here and CRF differences due to cancer treatment are a potential explanation. These differences remain to be investigated further since they have been reported in some studies^{21,43,44} but not in others.^{29,45,46} Physiological mechanisms such as cardiorespiratory deconditioning⁴⁷ have also been associated with CRF but were not evaluated in our study due to the additional constraints it would have placed on the experimental protocol. Several other neuromuscular parameters (e.g., voluntary activation and changes in muscular contractile properties) must also be considered in further studies. Some behavioral mechanisms have been related to CRF such as total physical activity^{19,10,23} or nutrition.^{21,48} There are several other biological/haematological factors that are related to CRF severity, including anemia,⁴⁹ inflammation,⁵⁰ cachexia⁵¹ or pain.²¹ The last group of CRF mechanisms is psychosocial. Bower et al.⁵² have reported that educational level, childhood adversity and trauma were predictors of CRF. Because catastrophizing has been associated with particularly high levels of CRF,⁵³ coping strategies to cancer diagnosis and treatment management could also be of influence. Future models should explore these in multidimensional models of CRF.

In this study, data from patients with breast cancer (which represent more than 70% of participants) as well as patients with other cancer types and treatment status were used. While this could be perceived as a limitation, our research team followed a chronic disease fatigue concept proposed by Menting et al.³⁸ where fatigue could be studied using a transdiagnostic approach rather than one that is disease-specific. Another possible limitation in the current study is the discrepancy between self-reported and objective measures of sleep disturbances.³⁴ Future investigations should rather implement objective sleep assessments or a combination of both, with a larger sample-size. One could also claimed that handgrip task is not functionally relevant as it involved only small muscle mass but it should be considered to represent an individual neuromuscular fatigability characteristic.⁵⁴ Finally, considering this is a model approach and that correlation is not causation, one should bear in mind that the parameters of CRF measured in the current study are not necessarily the cause of CRF.

Conclusion

To conclude, the neuromuscular fatigability represented by the handgrip isometric force asymptote is correlated to the CRF severity as previously proposed by Veni et al. Furthermore, this neuromuscular indicator significantly enhances the CRF variance explanation by 8% compared to anxiety/depression and sleep alone. The results of this study indicate that sleep disturbances, emotional symptoms and neuromuscular fatigability can account for 56% of the CRF variance in cancer patients during and after treatments. Although prospective data involving a larger sample size are required to adequately understand the magnitude of the relationship between emotional, neuromuscular and sleep parameters, the proposed model could be useful for supportive care professionals who seek to individually tailor interventions for CRF management.

Acknowledgements

The authors thank all participants for the time allowed and their involvement in this study.

Funding

This work was supported by the ‘Ligue nationale contre le cancer’ (thesis scholarship from first author) and the ‘Région Pays de la Loire’ (BIOCARE FActory project).

References

1. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-Related Fatigue, Version 1.2019. *National Comprehensive Cancer Network* 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf.
2. Weis J. Cancer-related fatigue: prevalence, assessment and treatment strategies. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11(4):441-446. doi:10.1586/erp.11.44
3. Minton O, Stone P. How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature. *Breast Cancer Res Treat.* 2008;112(1):5-13. doi:10.1007/s10549-007-9831-1
4. Seyidova-Khoshknabi D, Davis MP, Walsh D. Review article: a systematic review of cancer-related fatigue measurement questionnaires. *Am J Hosp Palliat Care.* 2011;28(2):119-129. doi:10.1177/1049909110381590
5. Giesinger JM, Kuijpers W, Young T, et al. Thresholds for clinical importance for four key domains of the EORTC QLQ-C30: physical functioning, emotional functioning, fatigue and pain. *Health Qual Life Outcomes.* 2016;14:87. doi:10.1186/s12955-016-0489-4
6. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.* 2014;11(10):597-609. doi:10.1038/nrclinonc.2014.127
7. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. *Oncologist.* 2007;12 Suppl 1:35-42. doi:10.1634/theoncologist.12-S1-35
8. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 1998;16(5):1689-1696. doi:10.1200/JCO.1998.16.5.1689
9. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol.* 2001;19(3):895-908. doi:10.1200/JCO.2001.19.3.895
10. Bødcher H, Bidstrup PE, Andersen I, et al. Fatigue trajectories during the first 8 months after breast cancer diagnosis. *Qual Life Res.* 2015;24(11):2671-2679. doi:10.1007/s11136-015-1000-0
11. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *J Clin Oncol.* 2011;29(26):3517-3522. doi:10.1200/JCO.2011.36.1154
12. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. *Support Care Cancer.* 2001;9(1):11-17.

13. Twomey R, Aboodarda SJ, Kruger R, Culos-Reed SN, Temesi J, Millet GY. Neuromuscular fatigue during exercise: Methodological considerations, etiology and potential role in chronic fatigue. *Neurophysiol Clin*. 2017;47(2):95-110. doi:10.1016/j.neucli.2017.03.002
14. Grisold W, Grisold A, Löscher WN. Neuromuscular complications in cancer. *J Neurol Sci*. 2016;367:184-202. doi:10.1016/j.jns.2016.06.002
15. Kisiel-Sajewicz K, Siemionow V, Seyidova-Khoshknabi D, et al. Myoelectrical manifestation of fatigue less prominent in patients with cancer related fatigue. *PLoS One*. 2013;8(12):e83636. doi:10.1371/journal.pone.0083636
16. Kisiel-Sajewicz K, Davis MP, Siemionow V, et al. Lack of muscle contractile property changes at the time of perceived physical exhaustion suggests central mechanisms contributing to early motor task failure in patients with cancer-related fatigue. *J Pain Symptom Manage*. 2012;44(3):351-361. doi:10.1016/j.jpainsymman.2011.08.007
17. Yavuzsen T, Davis MP, Ranganathan VK, et al. Cancer-related fatigue: central or peripheral? *J Pain Symptom Manage*. 2009;38(4):587-596. doi:10.1016/j.jpainsymman.2008.12.003
18. Twomey R, Martin T, Temesi J, Culos-Reed SN, Millet GY. Tailored exercise interventions to reduce fatigue in cancer survivors: study protocol of a randomized controlled trial. *BMC Cancer*. 2018;18(1):757. doi:10.1186/s12885-018-4668-z
19. Veni T, Boyas S, Beaune B, et al. Handgrip fatiguing exercise can provide objective assessment of cancer-related fatigue: a pilot study. *Support Care Cancer*. 2019;27(1):229-238. doi:10.1007/s00520-018-4320-0
20. Burnley M. Estimation of critical torque using intermittent isometric maximal voluntary contractions of the quadriceps in humans. *J Appl Physiol*. 2009;106(3):975-983. doi:10.1152/jappphysiol.91474.2008
21. Stone P, Richards M, A'Hern R, Hardy J. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. *Ann Oncol*. 2000;11(5):561-567. doi:10.1023/a:1008331230608
22. Lockefer JPM, De Vries J. What is the relationship between trait anxiety and depressive symptoms, fatigue, and low sleep quality following breast cancer surgery? *Psychooncology*. 2013;22(5):1127-1133. doi:10.1002/pon.3115
23. Humpel N, Iverson DC. Sleep quality, fatigue and physical activity following a cancer diagnosis. *Eur J Cancer Care (Engl)*. 2010;19(6):761-768. doi:10.1111/j.1365-2354.2009.01126.x

24. Tucker R. The anticipatory regulation of performance: the physiological basis for pacing strategies and the development of a perception-based model for exercise performance. *Br J Sports Med.* 2009;43(6):392-400. doi:10.1136/bjism.2008.050799
25. Kecke S, Ernst J, Eienkel J, Singer S, Hinz A. Psychometric Properties of the Fatigue Questionnaire EORTC QLQ-FA12 in a Sample of Female Cancer Patients. *J Pain Symptom Manage.* 2017;54(6):922-928. doi:10.1016/j.jpainsymman.2017.08.007
26. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
27. Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. *J Affect Disord.* 2010;126(3):335-348. doi:10.1016/j.jad.2010.01.067
28. Evans JD. *Straightforward statistics for the behavioral sciences* (Brooks/Col). Pacific Grove; 1996.
29. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol.* 2000;18(4):743-753. doi:10.1200/JCO.2000.18.4.743
30. De Vries J, Van der Steeg AF, Roukema JA. Trait anxiety determines depressive symptoms and fatigue in women with an abnormality in the breast. *Br J Health Psychol.* 2009;14(Pt 1):143-157. doi:10.1348/135910708X310200
31. Van Esch L, Roukema JA, Ernst MF, Nieuwenhuijzen GAP, De Vries J. Combined anxiety and depressive symptoms before diagnosis of breast cancer. *J Affect Disord.* 2012;136(3):895-901. doi:10.1016/j.jad.2011.09.012
32. Courtier N, Gambling T, Enright S, Barrett-Lee P, Abraham J, Mason MD. Psychological and immunological characteristics of fatigued women undergoing radiotherapy for early-stage breast cancer. *Support Care Cancer.* 2013;21(1):173-181. doi:10.1007/s00520-012-1508-6
33. Medysky ME, Temesi J, Culos-Reed SN, Millet GY. Exercise, sleep and cancer-related fatigue: Are they related? *Neurophysiol Clin.* 2017;47(2):111-122. doi:10.1016/j.neucli.2017.03.001
34. Martin T, Twomey R, Medysky ME, Temesi J, Culos-Reed SN, Millet GY. The Relationship between Fatigue and Actigraphy-Derived Sleep and Rest-Activity Patterns in Cancer Survivors. September 2019. doi:10.31236/osf.io/yswn8
35. Davis MP, Goforth HW. Long-term and short-term effects of insomnia in cancer and effective interventions. *Cancer J.* 2014;20(5):330-344. doi:10.1097/PPO.0000000000000071

36. Shochat T, Haimov I, Lavie P. Melatonin--the key to the gate of sleep. *Ann Med*. 1998;30(1):109-114. doi:10.3109/07853899808999392
37. McNeely ML, Courneya KS. Exercise programs for cancer-related fatigue: evidence and clinical guidelines. *J Natl Compr Canc Netw*. 2010;8(8):945-953.
38. Menting J, Tack CJ, Bleijenberg G, et al. Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychol*. 2018;37(6):530-543. doi:10.1037/hea0000598
39. 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(17):1840-1850. doi:10.1200/JCO.2013.53.4495
40. Pearson EJM, Morris ME, McKinstry CE. Cancer-related fatigue: appraising evidence-based guidelines for screening, assessment and management. *Support Care Cancer*. 2016;24(9):3935-3942. doi:10.1007/s00520-016-3228-9
41. Howell D, Keller-Olaman S, Oliver TK, et al. A pan-Canadian practice guideline and algorithm: screening, assessment, and supportive care of adults with cancer-related fatigue. *Curr Oncol*. 2013;20(3):e233-46. doi:10.3747/co.20.1302
42. de Lima FD, Battaglini CL, Chaves SN, et al. Effect of strength training and antioxidant supplementation on perceived and performance fatigability of breast cancer survivors - A randomized, double-blinded, placebo-controlled study. *Appl Physiol Nutr Metab*. April 2020. doi:10.1139/apnm-2020-0166
43. Cella D, Davis K, Breitbart W, Curt G, Fatigue Coalition. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol*. 2001;19(14):3385-3391. doi:10.1200/JCO.2001.19.14.3385
44. Woo B, Dibble SL, Piper BF, Keating SB, Weiss MC. Differences in fatigue by treatment methods in women with breast cancer. *Oncol Nurs Forum*. 1998;25(5):915-920.
45. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. *J Behav Med*. 1998;21(1):1-18.
46. Berglund G, Bolund C, Fornander T, Rutqvist LE, Sjöden PO. Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. *Eur J Cancer*. 1991;27(9):1075-1081. doi:10.1016/0277-5379(91)90295-o
47. Neil SE, Klika RJ, Garland SJ, McKenzie DC, Campbell KL. Cardiorespiratory and neuromuscular deconditioning in fatigued and non-fatigued breast cancer survivors. *Support Care Cancer*. 2013;21(3):873-881. doi:10.1007/s00520-012-1600-y

48. Norman K, Wirth R, Neubauer M, Eckardt R, Stobäus N. The bioimpedance phase angle predicts low muscle strength, impaired quality of life, and increased mortality in old patients with cancer. *J Am Med Dir Assoc.* 2015;16(2):173.e17-22. doi:10.1016/j.jamda.2014.10.024
49. Munch TN, Zhang T, Willey J, Palmer JL, Bruera E. The association between anemia and fatigue in patients with advanced cancer receiving palliative care. *J Palliat Med.* 2005;8(6):1144-1149. doi:10.1089/jpm.2005.8.1144
50. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res.* 2006;12(9):2759-2766. doi:10.1158/1078-0432.CCR-05-2398
51. Argilés JM, López-Soriano FJ, Busquets S. Mediators of cachexia in cancer patients. *Nutrition.* 2019;66:11-15. doi:10.1016/j.nut.2019.03.012
52. Bower JE, Asher A, Garet D, et al. Testing a biobehavioral model of fatigue before adjuvant therapy in women with breast cancer. *Cancer.* 2019;125(4):633-641. doi:10.1002/cncr.31827
53. Jacobsen PB, Andrykowski MA, Thors CL. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. *J Consult Clin Psychol.* 2004;72(2):355-361. doi:10.1037/0022-006X.72.2.355
54. Chartogne M, Rahmani A, Nicolon L, Jubeau M, Morel B. Neuromuscular fatigability amplitude and etiology are interrelated across muscles. *Exp Physiol.* August 2020. doi:10.1113/EP088682

Figure captions

Figure 1 Correlation between F_A and FA12 total score. *Black dots* represent the current study data and *grey squares* represent the Veni's data. *Black line* and *black dashed lines* represent the regression line and 95% confidence interval for the current study, respectively. *Grey line* and *grey dashed lines* represent the regression line and 95% confidence interval for the Veni's study, respectively.

Figure 2 Representation of the individual predicted and observed fatigue scores (*black dash*) in patients with cancer. *Black bar*, *light grey bar* and *dark grey bar* represent the components of predicted CRF related to the HADS score, the ΔF_A and the PSQI score, respectively. The height of the stacked bar represents the predicted fatigue score by the model



