Title

Prediction of evening fatigue severity in outpatients receiving chemotherapy: less may be more

Journal

Fatigue Biomedicine Health & Behavior, 9(1)

ISSN

2164-1846

Authors

Kober, Kord M

Roy, Ritu

Dhruva, Anand

et al.

Publication Date

2021-01-02

DOI

10.1080/21641846.2021.1885119

Peer reviewed

HHS Public Access

Author manuscript

Fatigue. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Fatigue. 2021 ; 9(1): 14–32. doi:10.1080/21641846.2021.1885119.

Prediction of evening fatigue severity in outpatients receiving chemotherapy: less may be more

Kord M. Kober, PhD[1,2,3], **Ritu Roy, MA**[2], **Anand Dhruva, MD**[4], **Yvette P. Conley, PhD**[5], **Raymond J. Chan, RN, PhD**[6,7], **Bruce Cooper, PhD**[1], **Adam Olshen, PhD**[2,8], **Christine Miaskowski, RN, PhD**[1,2]

[1]School of Nursing, University of California, San Francisco, USA

[2]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, USA

[3]Bakar Computational Health Sciences Institute, University of California, San Francisco, USA

[4]School of Medicine, University of California, San Francisco, USA

[5]School of Nursing, University of Pittsburgh, Pittsburgh, USA

[6]School of Nursing and Cancer and Palliative Care Outcomes Centre, Queensland University of Technology, Kelvin Grove, Australia

[7]Division of Cancer Services, Princess Alexandra Hospital, Metro South Hospital and Health Services, Woolloongabba, Australia

[8]Department of Epidemiology and Biostatistics, University of California, San Francisco, USA

Abstract

Background—Fatigue is the most common and debilitating symptom experienced by oncology patients undergoing chemotherapy. Little is known about patient characteristics that predict changes in fatigue severity over time.

Purpose—To predict the severity of evening fatigue in the week following the administration of chemotherapy using machine learning approaches.

Methods—Outpatients with breast, gastrointestinal, gynecological, or lung cancer (*N*=1217) completed questionnaires one week prior to and one week following administration of chemotherapy. Evening fatigue was measured with the Lee Fatigue Scale (LFS). Separate prediction models for evening fatigue severity were created using clinical, symptom, and psychosocial adjustment characteristics and either evening fatigue scores or individual fatigue item scores. Prediction models were created using two regression and three machine learning approaches.

Address correspondence to: Kord M. Kober, PhD, Assistant Professor, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-4658 (phone), 415-476-8899 (fax), kord.kober@ucsf.edu.

Disclosure of interest

The authors report no conflict of interest.

Results—Random forest (RF) models provided the best fit across all models. For the RF model using individual LFS item scores, two of the 13 individual LFS items (i.e., “worn out”, “exhausted”) were the strongest predictors.

Conclusion—This study is the first to use machine learning techniques to predict evening fatigue severity in the week following chemotherapy from fatigue scores obtained in the week prior to chemotherapy. Our findings suggest that the language used to assess clinical fatigue in oncology patients is important and that two simple questions may be used to predict evening fatigue severity.

Keywords

fatigue; cancer; chemotherapy; symptoms; patient-reported outcomes; machine learning; predictive model

Introduction

For the past 40 years,[1] cancer-related fatigue (CRF), a symptom that occurs in 14% to 96% of patients undergoing chemotherapy,[2,3] has been the subject of intense investigation. However, despite the high prevalence rate and negative impact of CRF on patients,[4–11] limited progress has been made on its treatment for a number of reasons. First, no universally accepted definition of CRF is available to guide research and clinical practice. One of the most commonly used definitions is that of the National Comprehensive Cancer Network (NCCN) which defines fatigue 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 and interferes with usual functioning”.[12]

Second, progress in fatigue assessment is challenging given the heterogeneity of CRF instruments.[13] In a 2019 systematic review of unidimensional and multidimensional scales to assess CRF,[13] 25 different instruments were evaluated. The number of items on these instruments ranged from 4 to 72, but validity and/or reliability information was missing for many of them. The authors concluded that the development of a “universally-defined tool kit for the assessment of CRF may help to clarify the concept of fatigue and promote a systematic approach to fatigue measurement”.[13]

Another important consideration in CRF assessment is the growing body of evidence suggesting that diurnal variations in fatigue severity are associated with different modifiable risk factors. For instance, evening fatigue severity is associated with higher levels of stress,[11] lower functional status, and higher levels of sleep disturbance and depression.[14] Recent work by our research team[14–17] and others[18–20] found that fatigue severity is highly variable over the course of a day and among individuals. More generally, the impact of CRF on patients is significant in terms of inability to tolerate treatments, lost productivity, lost days from work, and decreased quality of life.[4–8]

Regarding the management of CRF, the lack of a risk prediction model is another gap in our progress toward more effective management.[21–25] An accurate risk prediction model

could assist clinicians in identifying high risk patients and provide them with recommendations for activity modifying or non-pharmacologic interventions to prevent or reduce CRF.[26–28] Compared to traditional regression models, various machine learning (ML) approaches have the potential to improve the accuracy of prediction models. [29] Much of the research on risk modelling of symptom severity using ML approaches has focused on psychiatric symptoms.[30–34] Recently, we used ML techniques to predict the severity of depression, anxiety, and sleep disturbance in the week following the administration of chemotherapy.[35] This study demonstrated the potential of ML models to identify high risk patients, educate them about their symptom experience, and improve the timing of preventive and personalized symptom management interventions.

Only one CRF study has used supervised classification by filter methods and recursive feature elimination to identify and validate a specific gene cluster that predicted the risk for higher versus lower levels of fatigue in 44 patients with prostate cancer who underwent radiation therapy.[36] We found no studies that used ML approaches to predict CRF severity in patients undergoing chemotherapy. Given the complex nature of CRF, relatively large sample sizes may be needed to evaluate a larger number of predictors using ML methods. The goal of this study was to predict the severity of evening fatigue in the week following chemotherapy in a large and well-characterized sample of oncology outpatients. We hypothesized that a prediction model of evening fatigue severity that used ML approaches would provide improved predictive performance over traditional approaches.

Methods

This analysis is part of a larger longitudinal study that evaluated symptom clusters in oncology patients receiving chemotherapy. Details of this study are described elsewhere.[37]

Patients and settings

Inclusion criteria were as follows: patients were ≥18 years of age; had one of four cancer diagnoses (i.e., breast, gastrointestinal, gynecological, lung); had received at least one cycle of chemotherapy; would receive at least two additional cycles of chemotherapy; and were able to complete the study questionnaires in English. Recruitment occurred at two Comprehensive Cancer Centers, a Veterans Affairs hospital, and four community oncology programs. Eligible patients were approached by a research staff member in the infusion unit during their first or second cycle of chemotherapy to discuss study participation (Figure 1). Of the 2234 patients approached, 1343 agreed to participate and provided written informed consent. The most common reason for study refusal was generally feeling too overwhelmed with their cancer experience. The study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites.

Instruments

The complete list of predictors used in the analyses is provided in Supplemental File 1. Patients completed a demographics questionnaire and these validated measures: Alcohol Use Disorders Identification Test (AUDIT),[38] Karnofsky Performance Status (KPS) scale,[39]

Self-Administered Comorbidity Questionnaire (SCQ),[40] a smoking questionnaire,[41] 28-item Brief COPE scale,[42] NEO-Five Factor Inventory,[13] Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T),[43] Center for Epidemiological Studies-Depression (CES-D) scale,[44] General Sleep Disturbance Scale (GSDS),[45] Attentional Function Index (AFI),[46] a modified version of the Memorial Symptom Assessment Scale (MSAS),[47] Perceived Stress Scale (PSS),[48] Impact of Event Scale–Revised (IES-R),[49] Herth Hope Index (HHI),[50] and Conner-Davidson Resilience Scale (CD-RISC).[51] Medical records were reviewed for disease and treatment information.

Toxicity of each patient's chemotherapy regimen was rated using the MAX2 index. A MAX2 score is the average of the most frequent grade 4 hematologic toxicity and the most frequent grade 3 to 4 nonhematologic toxicity that correlates well with overall risk of severe toxicity for that regimen.[52–54] The emetogenicity of the chemotherapy regimens and types of antiemetic regimens were categorized using established clinical guidelines.[55] Eighteen laboratory values were included.

To assess evening fatigue severity in the week before (Time Point One, TP_1) and the week after (Time Point Two, TP_2) administration of chemotherapy, patients completed the 18-item LFS at each time point. The items are divided into a 13-item Fatigue Scale and a 5-item Energy Scale.[56] Each item was answered with a 0 to 10 numeric rating (Table 1). Total fatigue and energy scores were represented by the mean scores of each scale.[57,58] Higher scores indicate greater fatigue severity and higher levels of energy. Patients rated each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue)[6] and energy (i.e., ≥6.2 for morning energy, ≥3.5 for evening energy).[6] The predictor variable(s) of evening fatigue at TP_1 were quantified using either the LFS total score ($F1_{Total}$) or the score for each of the 13 LFS scale items ($F1_{Item}$). The outcome variable of evening fatigue at TP_2 was quantified using the LFS total score ($F2_{Total}$).

Data processing

Data from TP_1 were used to develop models to predict evening fatigue at TP_2 (Figure 2). An overview of our data processing and analysis approach is shown in Figure 3. We performed all analyses using R (version 3.6.2).[59] Data were collected from oncology patients at TP_1 (N=1343) and TP_2 (N=1217). Merging the two time points resulted in a dataset of 1217 patients which included 158 demographic and clinical predictor variables. After evaluating for missingness, 9 variables were excluded that had >15% missing values after observing a gap in the distribution of missingness around this number. The final dataset of potential predictors, using the LFS total score for evening fatigue at TP_1, included 145 variables (n=60 categorical, n=85 continuous). The final dataset using the 13 individual LFS scale items for evening fatigue at TP_1 included 157 predictor variables (n=60 categorical, n=97 continuous). Missing values were imputed using the k-nearest neighbors method [60,61] from the DataMiningWithR (DMwR) R package (version 0.4.1, http://www.dcc.fc.up.pt/~ltorgo/DataMiningWithR). A missing predictor variable was imputed by the weighted

average of that variable among the five nearest neighbors determined by Euclidean distance. Each weight was exp(−dist(x,j)), where dist(x,j) was the Euclidean distance between the case with missing predictor variable (x) and the neighbor (j). The continuous and categorical variables were imputed separately.

Prediction of Evening Fatigue in the Week Following Chemotherapy

In addition to traditional multivariable linear regression, three different supervised learning algorithms[62] were used to predict evening fatigue in the week following chemotherapy (TP_2). We applied two ensemble learning methods: (1) RPART [63] that implements the classification and regression trees (CART) method[63] using the rpart package in R (version 4.1–15, https://CRAN.R-project.org/package=rpart) and (2) RF[64] from the Random Forest package in R (version 4.6–14).[65] A third learning method, SVM, is a nonparametric, supervised, and kernel-based method that was implemented (http://www.csie.ntu.edu.tw/~cjlin/libsvm) using the kernlab package in R (version 0.9.29).[66]

Within the general models built using these algorithms, these parameter combinations were used: (1) linear regression with and without filtering, where filtering meant including only the variables with p-values of <0.05 from univariable fits.[67] The one-standard error rule was applied to choose the best model in RPART; (2) For RF, we varied the number of variables randomly sampled as candidates at each split in RF (i.e., mtry parameter), trying three values, p/2, p/3, and p/4, where p is the number of predictor variables. These values were 73, 48 and 36 when using $F1_{Total}$; and 79, 52 and 39 when using $F1_{Item}$; and (3) A polynomial kernel with SVM, varying the degree of the polynomial (1 to 3). Finally, we fit a null model that is the average of the $F2_{Total}$ values from the training set. It is the prediction of $F2_{Total}$ without any other variables in the model.

To avoid bias in prediction error estimates, models were fit in a cross-validated manner utilizing 10-fold cross validation to ensure that the same data that were used to fit a model were not used in its prediction.[68,69] To avoid the impact of a particular split in cross-validation, the cross-validation process was repeated 1000 times. The performance of each method was evaluated as the difference between the measured and predicted value at sampled points. For every round of cross-validation, the error in prediction was evaluated as the root mean square error (RMSE)[70] between the observed $F2_{Total}$ and the estimated $F2_{Total}$ from our model. To rank methods, the RMSEs (mRMSE) were averaged for each method across the 1000 repetitions of cross-validation.

Individual predictor variables in the multivariable models were ranked by assigning a variable importance score to each of them. The variable importance score estimated the contribution of each variable to the model as implemented in the Caret R package.[71] The importance scores were scaled to be between 0 and 100 for each method. Supplemental files are available from the figshare respository (http://figshare.com) and identified by the Digitial Object Identifier (https://doi.org/10.6084/m9.figshare.13150955).

Results

Patient characteristics

The sample (Table 2) was predominantly white, female, middle aged, and college-educated. Most were unemployed and not married. While patients' mean evening fatigue score at TP_1 was below the clinical cut-off, it increased to the cutoff level at TP_2.

Model evaluation and selection

Prediction of evening fatigue severity at TP_2 with $F1_{Total}$.—Using $F1_{Total}$ to predict evening fatigue severity at TP_2, the best performing RF model was mtry = p/2 (p = number of predictor variables); the best SVM model was a first degree polynomial; and the better linear model was filtered rather than unfiltered (Supplemental File 2). Across the final models, the RF method provided the best fit (mRMSE 1.53 (bootstrap CI 1.52–1.54); (Table 3, Figure 2, Supplemental Figure 1). All of the models predicted a mean $F2_{Total}$ (range: 5.61 to 5.65, Table 3) similar to the patient-reported mean of 5.62.

Of the estimated contribution of each of the top variables to the RF model (i.e., variable importance scores; Supplemental File 3) to predict evening fatigue severity at TP_2 (Table 4), $F1_{Total}$ was the most important predictor by a large margin. The next most important predictors were the GSDS excessive daytime sleepiness score, morning LFS total score, and evening Lee Energy Scale (LES) total score. As illustrated in the scatter plots of the most important predictors using RF (Supplemental Figure 2), $F2_{Total}$ was highly correlated with $F1_{Total}$ and less so with the next eight most important predictors.

Prediction of evening fatigue severity at TP_2 using $F1_{Item}$.—As the total score on the Evening LFS was the most important predictor, we evaluated models that used each of 13 LFS items as individual predictors (i.e., $F1_{Item}$) utilizing the same methods and characteristics but replacing $F1_{Total}$ with $F1_{Item}$ for evening fatigue. The best performing RF model was with mtry = p/4; the best SVM model was a third degree polynomial; and the better LM model was filtered rather than unfiltered (Supplemental File 4). Across the final models, we found that the RF method provided the best fit (mRMSE 1.53; bootstrap CI 1.52–1.54; Figure 2). All models predicted a mean $F2_{Total}$ of 5.61 to 5.69 similar to the patient-reported mean $F2_{Total}$ of 5.62 (Table 5). Of the 13 individual items in the evening LFS at time 1, the top two predictors in importance were the LFS scale items "worn out" and "exhausted" (Table 4, Supplemental Figure 4).

The RF method generated the best fitting models for both predictor datasets. Little difference in performance was found between the two RF models. The next-highest three predictors other than $F1_{Total}$ or $F1_{Item}$ in both of the RF models were the mean scores for excessive daytime sleepiness subscale of the GSDS, evening energy, and morning fatigue total severity. None of our models performed well in predicting extreme values of $F2_{Total}$ (Supplemental Figures 1 and 3).

Discussion

To our knowledge, this is the first study to use ML techniques to accurately predict the severity of evening fatigue during the week following administration of chemotherapy using total and individual item scores from the LFS obtained prior to the patients' second or third cycle of chemotherapy. In addition, this study is the first to evaluate the relative contributions of a diverse set of demographic, clinical, symptom, and psychological adjustment characteristics to predict evening fatigue severity in a large sample of oncology patients.

Use of single items to predict evening fatigue

Consistent with our *a priori* hypothesis, the RF model improved our ability to predict the severity of evening fatigue.[35] An important clinical finding is the ability of the RF model using single item scores from the evening LFS pre-chemotherapy to predict evening fatigue severity post-chemotherapy as accurately as the model using total evening LFS scores. Specifically, this finding suggests that clinicians can ask patients to rate (0–10) their level of feeling "worn out" or "exhausted" prior to chemotherapy to estimate their evening fatigue in the week following chemotherapy. The use of these most predictive single items may facilitate the assessment of evening fatigue in a busy oncology clinic, particularly in the absence of a patient symptom diary or smart electronic device.

Additional evidence regarding the clinical relevance of the "worn out" or "exhausted" items comes from several studies that used Rasch analyses to evaluate the psychometric properties of individual items on the LFS.[72–74] These studies evaluated patients with a variety of diagnoses (i.e., cancer,[72] HIV/AIDS,[73] stroke,[74] and osteoarthritis[74]) from the United States[72,73] and Norway[74]). Similar to our findings, these reports noted that a single fatigue item could be used to assess fatigue in the clinic [74]. That said, care should be taken to address cultural adaptation and linguistic validation to ensure conceptual equivalence across translations.[75,76]

Efforts are being made across the oncology community to integrate reliable, valid, and easy-to-use patient-reported outcome measures into routine clinical care.[77,78] In the NCCN guideline,[12] the recommendation is to screen for fatigue using a 0 (no fatigue) to 10 (worst fatigue you can imagine) rating. Our findings suggest that the word "fatigue" is less predictive than the more descriptive terms, "worn out" or "exhausted". In another instrument, the PROMIS Fatigue Item Bank, 95 items evaluate patients' fatigue experience and fatigue interference with daily life and function rated on a 1 (never) to 5 (always) Likert scale. It can be administered as either a computer adaptive test or as fixed-length short forms with a variable number of items.[79] While one question includes "exhausted" (i.e., How exhausted were you on average?), "worn out" is not used. Finally, the PRO-CTCAE is the newest fatigue measure that was designed to capture symptomatic adverse events directly from patients who are participating in clinical trials.[80,81] The measure has two fatigue items that are rated using a 7 day recall period on the dimensions of severity and interference. However, "worn out" and "exhausted" are not used. While these three self-report measures for fatigue are valid and reliable, they illustrate the lack of consensus that surrounds the assessment of fatigue.

Predictors of evening fatigue

Consistent with previous research, we found that mean scores for evening energy, morning fatigue, and excessive daytime sleepiness were the three top non-evening fatigue items of most importance across the two models. Morning fatigue as an important predictor of evening fatigue in our study is consistent with previous research indicating that morning and evening fatigue are distinct but related symptoms.[14–20,82–84] In addition, the current analysis confirmed that lower evening energy pre-chemotherapy is associated with increased fatigue following chemotherapy [85,86] and that energy is a distinct symptom.[87–90] While fatigue is associated with higher levels of sleep disturbance in oncology patients,[91–93] it is interesting to note that the excessive daytime sleepiness subscale score of the GSDS had higher importance in both models. Excessive daytime sleepiness is associated with increased napping and disruptions in the sleep-wake cycle which may lead to increases in evening fatigue.[94–96]

Limitations

While our final models performed well, predictions of low and high extremes of evening fatigue at TP_2 were less reliable due to insufficient data. Our attempts to fit more complex models to evaluate these extreme ranges (i.e., univariate and multivariate spline models with knots) did not improve predictive performance (data not shown). Because patients had already received one or two cycles of chemotherapy, further validation of our findings could be evaluated in patients prior to the initiation of chemotherapy. In addition, utilizing genomic data as potential predictors might improve the models and inform underlying biological mechanisms. Future prospective studies might be informative that either confirm or refute our findings in other patient samples such as patients undergoing surgery, radiation therapy, and other targeted therapies.

Conclusions

This study is the first to use ML methods to accurately predict evening fatigue severity following chemotherapy, with the strongest predictor being patient self-report of specific fatigue-related words, which could potentially become an important aspect of improving evaluation for precision health care.[97] Although the translational aspects of ML models are challenging[98], our findings suggest that the language used to assess fatigue is important. Specifically, oncology clinicians can ask patients two simple questions focused on the words ‘exhaustion’ and ‘worn-out’ to better predict patients’ evening fatigue severity across cycles of chemotherapy. Future research is needed to confirm these findings, perhaps in conjunction with additional phenotypic and molecular characteristics that may be used in predictive models of morning and evening fatigue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding details

This work was supported by the National Cancer Institute at the National Institute of Health under Grant CA134900, Grant CA233774 and Grant CA082103. Its contents are solely the responsibility of the authors and do

not necessarily represent the official views of the National Institutes of Health. Dr. Miaskowski is an American Cancer Society Clinical Research Professor.

Data availability statement

Data are available from the authors upon reasonable request.

Notes on contributors

Kord M. Kober is an Assistant Professor in the School of Nursing (SON) at the University of California, San Francisco (UCSF). He is a systems biologist and bioinformaticist. His program of research focuses on an evaluation of the mechanisms that underlie fatigue and peripheral neuropathy in oncology patients.

Ritu Roy is a Biostatistician at the UCSF Helen Diller Family Comprehensive Cancer Center.

Anand Dhruva is a Professor in the School of Medicine at UCSF and the Director of Education, UCSF Osher Center for Integrative Medicine. His program of research focuses on identifying integrating safe, effective, and individualized complementary healing approaches into cancer care and survivorship.

Yvette P. Conley is a Professor in the SON at the University of Pittsburgh. She earned her PhD in genetics. Her research interests are focused on the genetics of macular degeneration and subarachnoid hemorrhage, as well as the genomics of symptoms.

Raymond J. Chan is Professor in the SON and Cancer and Palliative Care Outcomes Centre at the Queensland University of Technology and in the Division of Cancer Services, Princess Alexandra Hospital, Metro South Hospital and Health Services.

Bruce Cooper is an Associate Professor and Senior Statistician in the SON at UCSF.

Adam Olshen is a Professor in the Dept. of Epidemiology and Biostatistics at UCSF and the Director of the Computational Biology and Informatics Core in the UCSF Helen Diller Family Comprehensive Cancer Center.

Christine Miaskowski is a Professor in the SON at UCSF. Her program of research focuses on the identification of phenotypic and molecular characteristics that place patients at higher risk for more severe symptom burden.

Abbreviations

AFI	Attentional Function Index
AUDIT	Alcohol Use Disorders Identification Test
CART	Classification and regression trees
CES-D	Center for Epidemiological Studies-Depression

CD-RISC	Conner-Davidson Resilience Scale
COPE	Coping Orientation to Problems Experienced
CRF	Cancer related fatigue
F1 $_{Total}$	Evening LFS at TP_1 total score
F1 $_{Item}$	Evening LFS at TP_1 scale items
F2 $_{Total}$	Evening LFS at TP_2 total score
GSDS	General Sleep Disturbance Scale
HHI	Herth Hope Index
IES-R	Impact of Event Scale–Revised
KPS	Karnofsky Performance Status
LFS	Lee Fatigue Scale
mRMSE	Mean RMSE
MSAS	Memorial Symptom Assessment Scale
ML	Machine learning
NRS	Numerical rating scale
NCCN	National Comprehensive Cancer Network
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PROMIS	Patient-Reported Outcomes Measurement Information System
PSS	Perceived Stress Scale
RF	Random forest
RPART	Recursive partitioning and regression trees
RMSE	Root mean square error
SCQ	Self-Administered Comorbidity Questionnaire
SD	Standard deviation
SI	Scale Items
STAI	Spielberger State-Trait Anxiety Inventory
SVM	Support vector machine

TP_1	Time Point 1
TP_2	Time Point 2

References

1. Haylock PJ, Hart LK. Fatigue in patients receiving localized radiation. Cancer Nurs 1979 12;2(6):461–7. [PubMed: 259440]
2. Prue G, Rankin J, Allen J, et al. Cancer-related fatigue: A critical appraisal. Eur J Cancer 2006 5;42(7):846–63. [PubMed: 16460928]
3. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer. 2006 2 15;106(4):751–8. [PubMed: 16400678]
4. Dhruva A, Lee K, Paul SM, et al. Sleep-wake circadian activity rhythms and fatigue in family caregivers of oncology patients. Cancer Nurs 2012 Jan-Feb;35(1):70–81. [PubMed: 21760489]
5. Fletcher BA, Schumacher KL, Dodd M, et al. Trajectories of fatigue in family caregivers of patients undergoing radiation therapy for prostate cancer. Res Nurs Health 2009 4;32(2):125–39. [PubMed: 19072846]
6. Fletcher BS, Paul SM, Dodd MJ, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. J Clin Oncol 2008 2 1;26(4):599–605. [PubMed: 18235118]
7. Gupta D, Lis CG, Grutsch JF. The relationship between cancer-related fatigue and patient satisfaction with quality of life in cancer. J Pain Symptom Manage 2007 7;34(1):40–7. [PubMed: 17532179]
8. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Seminars in hematology 1997 7;34(3 Suppl 2):4–12. [PubMed: 9253778]
9. Bower JE, Ganz PA. Symptoms: Fatigue and Cognitive Dysfunction. Adv Exp Med Biol 2015;862:53–75. [PubMed: 26059929]
10. Winningham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience: the state of the knowledge. Oncol Nurs Forum 1994 Jan-Feb;21(1):23–36. [PubMed: 8139999]
11. Wright F, Kober KM, Cooper BA, et al. Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. Support Care Cancer 2020 10;28(10):4697–4706. [PubMed: 31956947]
12. Berger AM, Mooney K, Banerjee A, et al. NCCN Guidelines Version 1.2020 - Cancer-Related Fatigue: National Comprehensive Cancer Network, Inc; 2020 [updated 02/21/20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf
13. Al Maqbali M, Hughes C, Gracey J, et al. Quality assessment criteria: psychometric properties of measurement tools for cancer related fatigue. Acta Oncol 2019 9;58(9):1286–1297. [PubMed: 31204538]
14. Dhruva A, Aouizerat BE, Cooper B, et al. Differences in morning and evening fatigue in oncology patients and their family caregivers. Eur J Oncol Nurs 2013 12;17(6):841–8. [PubMed: 24012189]
15. Kober KM, Cooper BA, Paul SM, et al. Subgroups of chemotherapy patients with distinct morning and evening fatigue trajectories. Support Care Cancer 2016 4;24(4):1473–85. [PubMed: 26361758]
16. Wright F, D'Eramo Melkus G, Hammer M, et al. Predictors and Trajectories of Morning Fatigue Are Distinct From Evening Fatigue. J Pain Symptom Manage 2015 8;50(2):176–89. [PubMed: 25828559]
17. Wright F, D'Eramo Melkus G, Hammer M, et al. Trajectories of Evening Fatigue in Oncology Outpatients Receiving Chemotherapy. J Pain Symptom Manage 2015 8;50(2):163–75. [PubMed: 25828560]
18. Molassiotis A, Chan CW. Fatigue patterns in Chinese patients receiving radiotherapy. Eur J Oncol Nurs 2004 12;8(4):334–40. [PubMed: 15550363]

19. Jim HS, Small B, Faul LA, et al. Fatigue, depression, sleep, and activity during chemotherapy: daily and intraday variation and relationships among symptom changes. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 2011 12;42(3):321–33. [PubMed: 21785899]
20. Dimsdale JE, Ancoli-Israel S, Ayalon L, et al. Taking fatigue seriously, II: variability in fatigue levels in cancer patients. Psychosomatics 2007 May-Jun;48(3):247–52. [PubMed: 17478594]
21. Hsiao CP, Wang D, Kaushal A, et al. Mitochondria-related gene expression changes are associated with fatigue in patients with nonmetastatic prostate cancer receiving external beam radiation therapy [Research Support, N.I.H., Intramural]. Cancer Nurs 2013 May-Jun;36(3):189–97. [PubMed: 23047795]
22. Saligan LN, Olson K, Filler K, et al. The biology of cancer-related fatigue: a review of the literature. Support Care Cancer 2015 8;23(8):2461–78. [PubMed: 25975676]
23. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nature reviews Clinical oncology 2014 10;11(10):597–609.
24. Barsevick A, Frost M, Zwinderman A, et al. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. Qual Life Res 2010 12;19(10):1419–27. [PubMed: 20953908]
25. Landmark-Hoyvik H, Reinertsen KV, Loge JH, et al. The genetics and epigenetics of fatigue [Review]. PM & R : the journal of injury, function, and rehabilitation 2010 5;2(5):456–65.
26. Meneses-Echavez JF, Gonzalez-Jimenez E, Ramirez-Velez R. Effects of Supervised Multimodal Exercise Interventions on Cancer-Related Fatigue: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomed Res Int 2015;2015:328636. [PubMed: 26167483]
27. Tomlinson D, Diorio C, Beyene J, et al. Effect of exercise on cancer-related fatigue: a meta-analysis. Am J Phys Med Rehabil 2014 8;93(8):675–86. [PubMed: 24743466]
28. Cramer H, Lauche R, Klose P, et al. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. The Cochrane database of systematic reviews 2017 1 3;1:CD010802. [PubMed: 28045199]
29. Chen JH, Asch SM. Machine Learning and Prediction in Medicine - Beyond the Peak of Inflated Expectations. N Engl J Med 2017 6 29;376(26):2507–2509. [PubMed: 28657867]
30. de Jong S, Newhouse SJ, Patel H, et al. Immune signatures and disorder-specific patterns in a cross-disorder gene expression analysis. Br J Psychiatry 2016 9;209(3):202–8. [PubMed: 27151072]
31. Kautzky A, Dold M, Bartova L, et al. Refining Prediction in Treatment-Resistant Depression: Results of Machine Learning Analyses in the TRD III Sample. J Clin Psychiatry 2017 12 5;79(1).
32. Oh J, Yun K, Hwang JH, et al. Classification of Suicide Attempts through a Machine Learning Algorithm Based on Multiple Systemic Psychiatric Scales. Frontiers in psychiatry 2017;8:192. [PubMed: 29038651]
33. Kessler RC, van Loo HM, Wardenaar KJ, et al. Testing a machine-learning algorithm to predict the persistence and severity of major depressive disorder from baseline self-reports. Mol Psychiatry 2016 10;21(10):1366–71. [PubMed: 26728563]
34. Jin H, Wu S, Di Capua P. Development of a Clinical Forecasting Model to Predict Comorbid Depression Among Diabetes Patients and an Application in Depression Screening Policy Making. Prev Chronic Dis 2015 9 3;12:E142. [PubMed: 26334714]
35. Papachristou N, Puschmann D, Barnaghi P, et al. Learning from data to predict future symptoms of oncology patients. PLoS One 2018;13(12):e0208808. [PubMed: 30596658]
36. Saligan LN, Fernandez-Martinez JL, deAndres-Galiana EJ, et al. Supervised classification by filter methods and recursive feature elimination predicts risk of radiotherapy-related fatigue in patients with prostate cancer. Cancer Inform 2014;13:141–52. [PubMed: 25506196]
37. Miaskowski C, Cooper BA, Aouizerat B, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. Eur J Cancer Care (Engl) 2016 1 18.
38. Babor T, Higgins-Biddle J, Saunders J, et al. The alcohol use disorders identification test (AUDIT): Guidelines for use in primary care 2001.
39. Karnofsky D Performance scale. New York: Plenum Press; 1977. (Kennealey GT, Mitchell MS, editors. Factors that influence the therapeutic response in cancer: a comprehensive treatise).

40. Sangha O, Stucki G, Liang MH, et al. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis and rheumatism 2003 4 15;49(2):156–63. [PubMed: 12687505]
41. Kozlowski LT, Porter CQ, Orleans CT, et al. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. Drug Alcohol Depend 1994;34(3):211–6. [PubMed: 8033758]
42. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 1997;4(1):92–100. [PubMed: 16250744]
43. Spielberger C, Gorsuch R, Suchene R, et al. Manual for the state-anxiety (Form Y): Self Evaluation Questionnaire. Palo Alto, CA.
44. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement 1977;1:385–401.
45. Lee KA. Self-reported sleep disturbances in employed women. Sleep 1992 12;15(6):493–8. [PubMed: 1475563]
46. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index--a self-report cognitive measure. Psychooncology 2011 2;20(2):194–202. [PubMed: 20213858]
47. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. European Journal of Cancer 1994;30(9):1326–1336.
48. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983 12;24(4):385–96. [PubMed: 6668417]
49. Weiss DS, Marmar CR. The Impact of Event Scale - Revised. New York: Guilford Press; 1997. (Wilson J, Keane TM, editors. Impact of Event Scale - Revised).
50. Herth K Abbreviated instrument to measure hope: development and psychometric evaluation. J Adv Nurs 1992 10;17(10):1251–9. [PubMed: 1430629]
51. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety 2003;18(2):76–82. [PubMed: 12964174]
52. Extermann M, Bonetti M, Sledge GW, et al. MAX2--a convenient index to estimate the average per patient risk for chemotherapy toxicity; validation in ECOG trials. Eur J Cancer 2004 5;40(8):1193–8. [PubMed: 15110883]
53. Extermann M, Reich RR, Sehovic M. Chemotoxicity recurrence in older patients: Risk factors and effectiveness of preventive strategies-a prospective study. Cancer 2015 9 1;121(17):2984–92. [PubMed: 26033177]
54. Aapro M, Extermann M, Repetto L. Evaluation of the elderly with cancer. Annals of Oncology 2000;11.
55. Singh KP, Kober KM, Dhruva AA, et al. Risk Factors Associated With Chemotherapy-Induced Nausea in the Week Before the Next Cycle and Impact of Nausea on Quality of Life Outcomes. J Pain Symptom Manage 2018 9;56(3):352–362. [PubMed: 29857180]
56. Lee KA. The author replies. Psychiatry Res 1993;46(2):209–210.
57. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991 3;36(3):291–8. [PubMed: 2062970]
58. Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manage 1999 5;17(5):320–32. [PubMed: 10355211]
59. Team RC. R: A Language and Environment for Statistical Computing Vienna, Austria: R Foundation for Statistical Computing; 2019.
60. Andridge RR, Little RJ. A Review of Hot Deck Imputation for Survey Non-response. Int Stat Rev 2010 4;78(1):40–64. [PubMed: 21743766]
61. Beretta L, Santaniello A. Nearest neighbor imputation algorithms: a critical evaluation. BMC Med Inform Decis Mak 2016 7 25;16 Suppl 3:74. [PubMed: 27454392]
62. Traverso A, Dankers F, Osong B, et al. Diving Deeper into Models. In: Kubben P, Dumontier M, Dekker A, editors. Fundamentals of Clinical Data Science Cham (CH)2019. p. 121–133.

63. Breiman L, Friedman J, Olshen R, et al. Classification and Regression Trees New York: Wadsworth; 1984.
64. Breiman L Random forests. Machine Learning 2001;45(1):5–32.
65. Liaw A, Weiner M. Classification and Regression by randomForest. R News 2002;2(3):18–22.
66. Karatzoglou A, Smola A, Hornik K, et al. kernlab - An S4 Package for Kernel Methods in R. Journal of Statistical Software 2004;11(9):1–20.
67. Smialowski P, Frishman D, Kramer S. Pitfalls of supervised feature selection. Bioinformatics 2010 2 1;26(3):440–3. [PubMed: 19880370]
68. Dankers F, Traverso A, Wee L, et al. Prediction Modeling Methodology. In: Kubben P, Dumontier M, Dekker A, editors. Fundamentals of Clinical Data Science Cham (CH)2019. p. 101–120.
69. Rodriguez JD, Perez A, Lozano JA. Sensitivity analysis of kappa-fold cross validation in prediction error estimation. IEEE Trans Pattern Anal Mach Intell 2010 3;32(3):569–75. [PubMed: 20075479]
70. Chai T, Draxler RR. Root mean square error (RMSE) or mean absolute error (MAE)? – Arguments against avoiding RMSE in the literature. Geoscientific Model Development 2014;7(3):1247–1250.
71. Kuhn M Building Predictive Models in R Using the caret Package 2008. 2008 2008–11-10;28(5):26.
72. Lerdal A, Kottorp A, Gay C, et al. A Rasch Analysis of Assessments of Morning and Evening Fatigue in Oncology Patients Using the Lee Fatigue Scale. J Pain Symptom Manage 2016 6;51(6):1002–12. [PubMed: 26975624]
73. Lerdal A, Kottorp A, Gay CL, et al. Development of a short version of the Lee Visual Analogue Fatigue Scale in a sample of women with HIV/AIDS: a Rasch analysis application. Qual Life Res 2013 8;22(6):1467–72. [PubMed: 23054493]
74. Bragstad LK, Lerdal A, Gay CL, et al. Psychometric properties of a short version of Lee Fatigue Scale used as a generic PROM in persons with stroke or osteoarthritis: assessment using a Rasch analysis approach. Health Qual Life Outcomes 2020 6 5;18(1):168. [PubMed: 32503548]
75. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health 2005 Mar-Apr;8(2):94–104. [PubMed: 15804318]
76. Johansson S, Kottorp A, Lee KA, et al. Can the Fatigue Severity Scale 7-item version be used across different patient populations as a generic fatigue measure--a comparative study using a Rasch model approach. Health Qual Life Outcomes 2014 2 22;12:24. [PubMed: 24559076]
77. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol 2007 11 10;25(32):5106–12. [PubMed: 17991929]
78. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014 9;106(9).
79. Cella D, Lai JS, Jensen SE, et al. PROMIS Fatigue Item Bank had Clinical Validity across Diverse Chronic Conditions. J Clin Epidemiol 2016 5;73:128–34. [PubMed: 26939927]
80. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015 11;1(8):1051–9. [PubMed: 26270597]
81. Kluetz PG, Chingos DT, Basch EM, et al. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book 2016;35:67–73. [PubMed: 27249687]
82. Wright F, Dunn LB, Paul SM, et al. Morning Fatigue Severity Profiles in Oncology Outpatients Receiving Chemotherapy. Cancer Nurs 2019 7 17;42(5):355–364. [PubMed: 30024437]
83. Wright F, Cooper BA, Conley YP, et al. Distinct Evening Fatigue Profiles in Oncology Outpatients Receiving Chemotherapy. Fatigue 2017;5(3):131–144. [PubMed: 29725554]
84. Jim HS, Small B, Faul LA, et al. Fatigue, depression, sleep, and activity during chemotherapy: daily and intraday variation and relationships among symptom changes. Ann Behav Med 2011 12;42(3):321–33. [PubMed: 21785899]

85. Aouizerat BE, Dhruva A, Paul SM, et al. Phenotypic and Molecular Evidence Suggests That Decrements in Morning and Evening Energy Are Distinct but Related Symptoms. J Pain Symptom Manage 2015 11;50(5):599–614 e3. [PubMed: 26031709]

86. Abid H, Kober KM, Smoot B, et al. Common and Distinct Characteristics Associated With Trajectories of Morning and Evening Energy in Oncology Patients Receiving Chemotherapy. J Pain Symptom Manage 2017 1 04.

87. Lerdal A A concept analysis of energy. Its meaning in the lives of three individuals with chronic illness. Scand J Caring Sci 1998;12(1):3–10. [PubMed: 9601440]

88. O'Connor PJ. Mental energy: Assessing the mood dimension. Nutr Rev 2006 7;64(7 Pt 2):S7–9. [PubMed: 16910215]

89. Lerdal A A theoretical extension of the concept of energy through an empirical study. Scand J Caring Sci 2002 6;16(2):197–206. [PubMed: 12000674]

90. Loy BD, Cameron MH, O'Connor PJ. Perceived fatigue and energy are independent unipolar states: Supporting evidence. Med Hypotheses 2018 4;113:46–51. [PubMed: 29523293]

91. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al. Cancer-related fatigue and sleep disorders. Oncologist 2007;12 Suppl 1:35–42. [PubMed: 17573454]

92. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. Eur J Cancer Care (Engl) 2001 12;10(4):245–55. [PubMed: 11806675]

93. Liu L, Rissling M, Natarajan L, et al. The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. Sleep 2012 2 1;35(2):237–45. [PubMed: 22294814]

94. Barsevick AM, Whitmer K, Sweeney C, et al. A pilot study examining energy conservation for cancer treatment-related fatigue. Cancer Nurs 2002 10;25(5):333–41. [PubMed: 12394560]

95. Barsevick AM, Dudley W, Beck S, et al. A randomized clinical trial of energy conservation for patients with cancer-related fatigue. Cancer 2004 3 15;100(6):1302–10. [PubMed: 15022300]

96. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw 2015 8;13(8):1012–39. [PubMed: 26285247]

97. Glasgow RE, Kwan BM, Matlock DD. Realizing the full potential of precision health: The need to include patient-reported health behavior, mental health, social determinants, and patient preferences data. J Clin Transl Sci 2018 6;2(3):183–185. [PubMed: 30370072]

98. Sendak MP, D'Arcy J, Kashyap S, et al. A path for translation of machine learning products into healthcare delivery. EMJ Innov 2020.

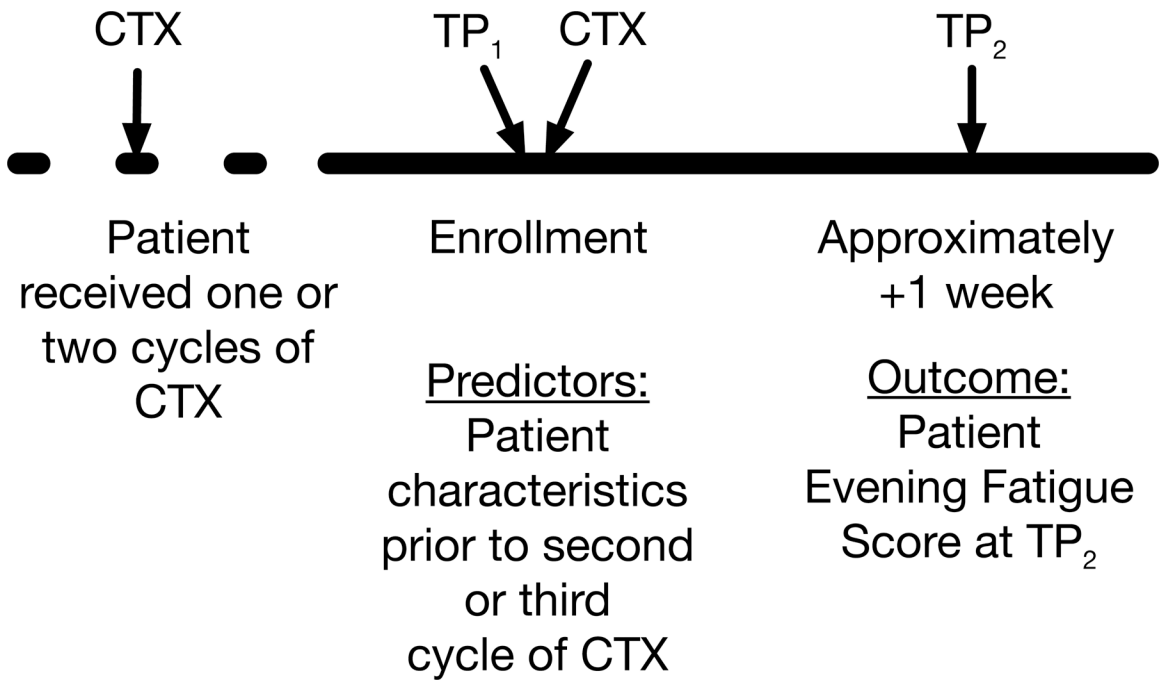

Figure 1.

Timeline depicting when the predictor variables at Time Point 1 (TP_1) and outcome variable at Time Point 2 (TP_2) were collected. All patients were enrolled prior to their second or third cycle of chemotherapy (chemotherapy). TP_1 occurred at enrollment into this study and prior to the patient's second or third cycle of chemotherapy. TP_2 occurred approximately one week (+1) after the enrollment visit.

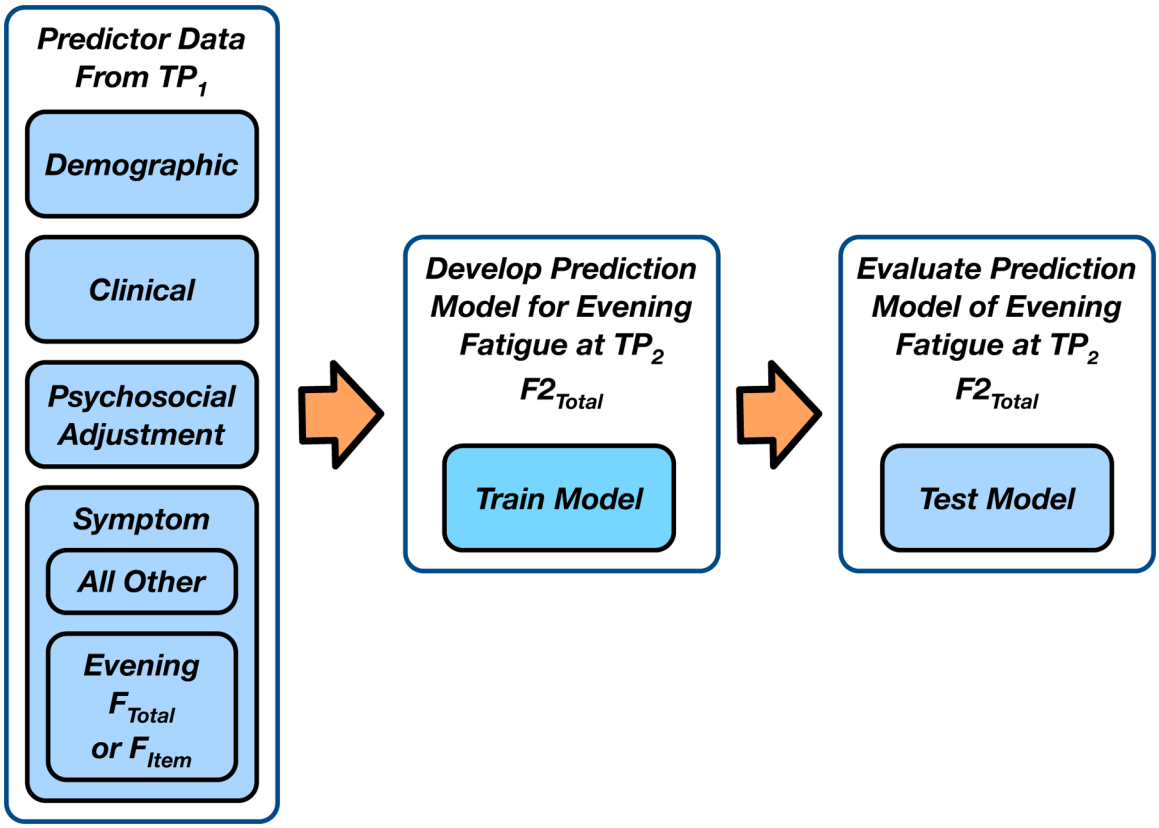

Figure 2.

A depiction of the data collected at Time Point 1 (TP_1) used to develop the models to predict evening fatigue at Time Point 2 (TP_2). Evening fatigue at TP_1 is characterized as either the total score ($F1_{Total}$) or scale items ($F1_{Item}$) of the Lee Fatigue Scale.

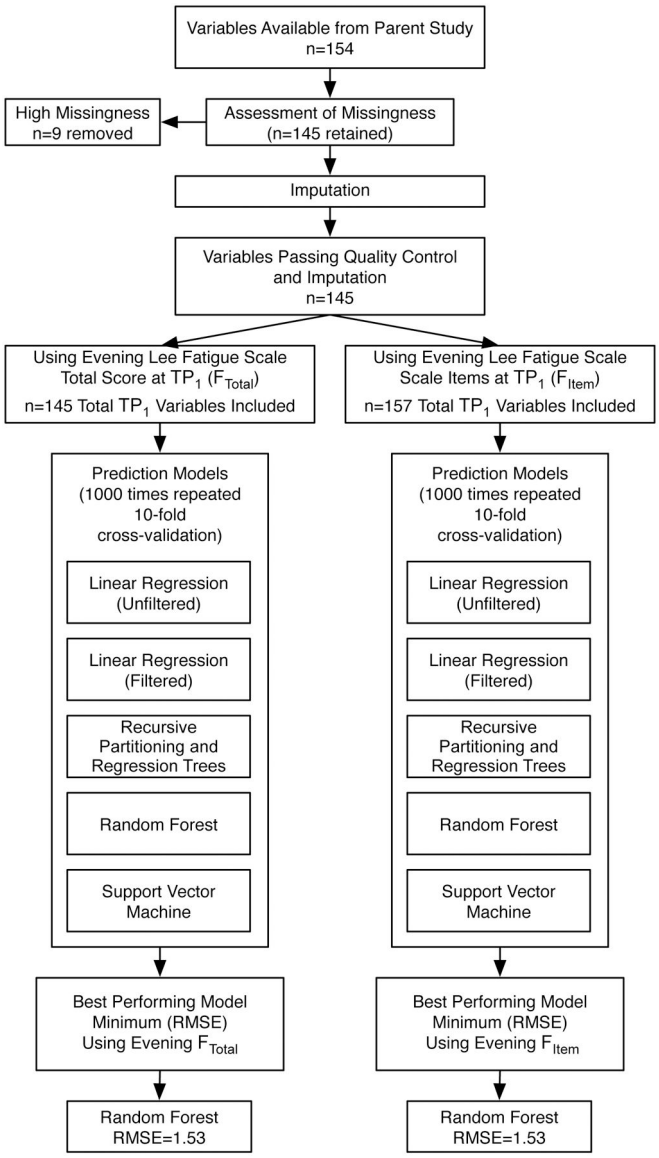

Figure 3.

Overview of the analysis approached used to develop prediction models of evening fatigue at Time Point 2 from demographic and clinical characteristics at Time Point 1 (TP_1).

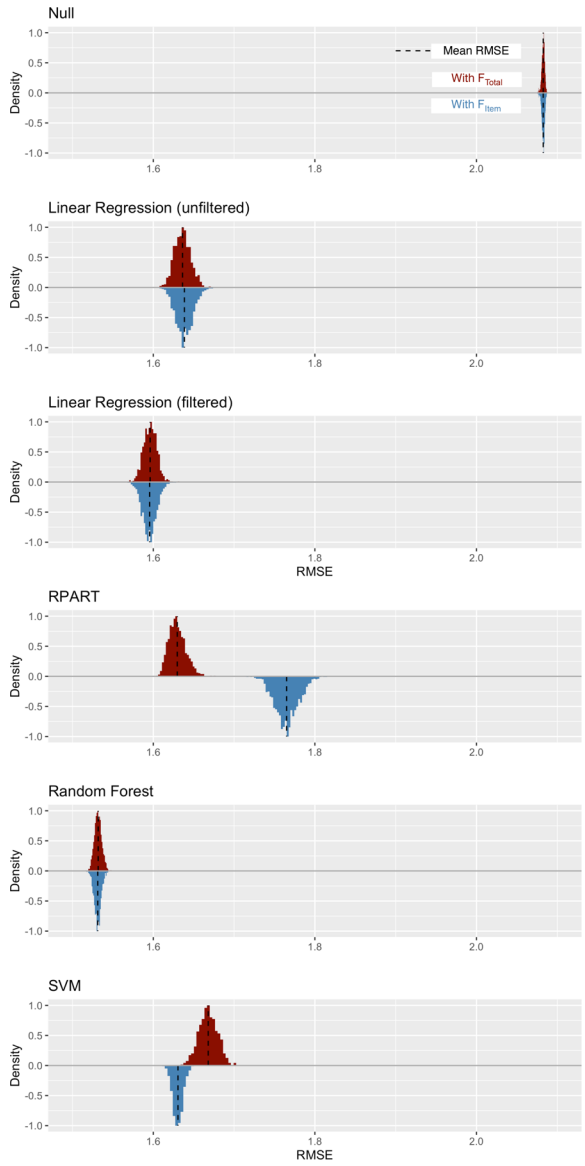

Figure 4.

Comparisons of the performance of prediction models for evening fatigue one week following the administration of chemotherapy using demographic, clinical and psychosocial adjustment characteristics assessed prior to the at administration of chemotherapy.

Abbreviations: F1 $_{Item}$, Evening Lee Fatigue Scale Item Score at Time Point 1; F1 $_{Item}$, Evening Lee Fatigue Scale Total Score at Time Point 1; RMSE, root mean square error; TS, total score; SI, scale items.

Table 1.

Individual items on the Lee Fatigue Scale (LFS) and summary of other studies that used items from the LFS.

	Description	Lerdal *et al.*, 2013[1]	Lerdal *et al.*, 2016[2]	Bragstad *et al.*, 2020[3]
	Study summary			
	Instrument	5-item LFS	10-item LFS	3-item LFS
	Fatigue	Evening, Morning	Evening	Not specified
	Study sample	Women with HIV	Patients with cancer	People with stroke and osteoarthritis
	Country	US	US	Norway
Item No.	LFS Items			
1	Tired	*	*	*
2	Sleep	-	*	
3	Drowsy	-	*	
4	Fatigued	*	*	*
5	Worn out^	*	*	*
11	Bushed	*	*	
12	Exhausted^	*	*	
13	Keeping my eyes open	-	*	
14	Moving my body	-	-	
15	Concentrating	-	-	
16	Carrying on a conversation	-	-	-
17	Desire to close my eyes	-	*	-
18	Desire to lie down	-	*	

Abbreviations: HIV, Human immunodeficiency virus.

Empty space, Not evaluated in Rasch analysis

-, Not retained after Rasch analysis

*, Retained after Rasch analysis

^, Top predictors of evening fatigue one week following chemotherapy in our analysis using LFS scale items for the week prior to administration of chemotherapy.

References

1. Lerdal A, Kottorp A, Gay CL, et al. Development of a short version of the Lee Visual Analogue Fatigue Scale in a sample of women with HIV/AIDS: a Rasch analysis application. Qual Life Res. 2013 Aug;22(6):1467–72.

2. Lerdal A, Kottorp A, Gay C, et al. A Rasch Analysis of Assessments of Morning and Evening Fatigue in Oncology Patients Using the Lee Fatigue Scale. J Pain Symptom Manage. 2016 Jun;51(6):1002–12.

3. Bragstad LK, Lerdal A, Gay CL, et al. Psychometric properties of a short version of Lee Fatigue Scale used as a generic PROM in persons with stroke or osteoarthritis: assessment using a Rasch analysis approach. Health Qual Life Outcomes. 2020 Jun 5;18(1):168.

Table 2.

Demographic, Clinical, Symptom, and Psychosocial Adjustment Characteristics of the Patients at Timepoint 1 (n=1217)

Demographic Characteristics	
Age (years; mean (SD))	56.9 (12.3)
Gender (% female (n))	78.0 (950)
Ethnicity (% (n))	
White	69.6 (836)
Black Non-Hispanic	6.8 (82)
Asian/Pacific Islander	12.8 (154)
Hispanic/Mixed/Other	10.8 (130)
Education (years; mean (SD))	16.2 (3.0)
Married or partnered (% yes (n))	59.1 (706)
Lives alone (% yes (n))	21.6 (259)
Currently employed (% yes (n))	35.2 (425)
Child care responsibilities (% yes (n))	22.3 (267)
Income (% (n))	
Less than $30,000	18.5 (201)
$30,000 to <$70,000	21.0 (229)
$70,000 to < $100,000	16.6 (181)
More than $100,000	43.8 (477)
Clinical Characteristics	
Self-administered Comorbidity Questionnaire score (mean (SD))	5.4 (3.2)
Body mass index (kg/m^2; mean (SD))	26.2 (5.7)
Hemoglobin (gm/dL; mean (SD))	11.5 (1.4)
Karnofsky Performance Status score (mean (SD))	80.1 (12.5)
Exercise on a regular basis (% yes (n))	70.7 (843)
Cancer diagnosis	
Breast	40.8 (496)
Gastrointestinal	30.3 (369)
Gynecological	17.3 (211)
Lung	11.6 (141)
Time since cancer diagnosis (years; mean (SD))	1.9 (3.8)
Number prior cancer treatments (mean (SD))	1.6 (1.5)
CTX toxicity MAX2 score (mean (SD))	0.2 (0.1)
Number of metastatic sites including lymph node involvement (mean (SD))	1.2 (1.2)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.8 (1.1)
Symptom Characteristics	
Lee Fatigue Scale: evening fatigue total score (mean (SD))	5.3 (2.1)
Lee Fatigue Scale: morning fatigue total score (mean (SD))	3.1 (2.3)
Lee Fatigue Scale: evening energy total score (mean (SD))	3.5 (2.0)
Lee Fatigue Scale: morning energy total score (mean (SD))	4.4 (2.3)

Demographic Characteristics	
Pain present (% yes (n))	72.2 (869)
Psychosocial Adjustment Characteristics	
Center for Epidemiological Studies-Depression Scale total score (mean (SD))	12.7 (9.7)
General Sleep Disturbance Scale score (mean (SD))	52.3 (20.4)
Spielberger Trait Anxiety score (mean (SD))	35.1 (10.5)
Spielberger State Anxiety score (mean (SD))	33.8 (12.4)
Conner-Davidson Resilience Scale (mean (SD))	30.1 (6.3)
Attentional Function Index (mean (SD))	6.4 (1.8)
Perceived Stress Scale (mean (SD))	18.4 (8.2)
Impact of Event Scale–Revised (mean (SD))	18.5 (13.0)
Herth Hope Index (mean (SD))	40.3 (5.4)

Abbreviations: CTX, chemotherapy; gm/dL, grams per deciliter; kg/m^2, kilograms per meters squared; SD, standard deviation; RT, radiation therapy.

Table 3.

Performance of the final models for predicting evening fatigue in the week following the administration of chemotherapy using evening fatigue at time point 1 measured as the total score of the Lee Fatigue Scale.

Method	Mean Predicted $F2_{Total}$	SD Predicted $F2_{Total}$	Mean RMSE	Relative Performance[a]	2.5%[b]	97.5%[b]
Random forest	5.61	1.31	1.53	0.0%	1.52	1.54
Linear regression (Filtered)	5.62	1.52	1.60	4.2%	1.58	1.61
RPART	5.62	1.32	1.63	6.4%	1.61	1.65
Linear regression (Unfiltered)	5.62	1.57	1.64	6.8%	1.62	1.66
Support vector machine	5.65	1.66	1.67	8.9%	1.65	1.69
Mean (null model)	5.62	0.00	2.08	36.0%	2.08	2.09

Abbreviations: ELFS, Evening Lee Fatigue Scale; $F2_{Total}$, ELFS total score at time point 2; RMSE, root mean square error; RPART, recursive partitioning and regression Trees; SD, standard deviation

[a] The ratio of (RSEM model/RSME RF model) expressed as a percentage.

[b] RMSE percentiles based on simulation (replicate count = 1000).

Table 4.

The top fifteen predictors with highest variable importance for random forest models using Evening LFS Total Score or Evening LFS Items at Time 1.

	RF Model Using Evening LFS Total Score at T1		RF Model Using Evening LFS Scale Items at T1	
Rank	**T1 Predictor**	**Score[a]**	**T1 Predictor**	**Score[a]**
1	Evening $F1_{Total}$	100.00	Evening $F1_{Item}$ - Worn out	100.00
2	GSDS Excessive Daytime Sleepiness - MS	11.68	Evening $F1_{Item}$ - Exhausted	93.52
3	Morning LFS TS	11.20	Evening $F1_{Item}$ - Fatigued	63.81
4	Evening LES TS	8.81	Evening $F1_{Item}$ - Concentrating	56.62
5	GSDS Total - Sum Score	5.46	Evening $F1_{Item}$ - Bushed	47.08
6	NEO-FFI Openness Subscale Raw Score	4.45	Evening $F1_{Item}$ - Desire to lie down	45.14
7	Number of MSAS Symptoms Out of 38	3.47	Evening $F1_{Item}$ - Keeping my eyes open	34.23
8	New AFI Attentional Lapses Subscale	3.23	Evening $F1_{Item}$ - Desire to close my eyes	32.51
9	White blood cell count	2.80	Evening $F1_{Item}$ - Conversation Effort	29.02
10	Age	2.73	Evening $F1_{Item}$ - Moving my body	23.41
11	Morning LES TS	2.59	Evening LES TS	18.39
12	Mean corpuscular hemoglobin	2.57	Morning LFS TS	16.71
13	Time from Diagnosis to Start of Study in Years	2.55	GSDS Excessive Daytime Sleepiness - MS	16.43
14	New AFI TS	2.47	Evening $F1_{Item}$ - Drowsy	16.42
15	CESD Somatic Subscale	2.46	Evening $F1_{Item}$ - Tired	13.99

Abbreviations: AFI, Attentional Function Index; CARET, Classification And REgression Training; CESD, Center for Epidemiological Studies-Depression scale; $F1_{Item}$, Evening LFS item at time point 1; $F1_{Total}$, Evening LFS total score at time point 1; GSDS, General Sleep Disturbance Scale; KPS, Karnofsky Performance Status; LES, Lee Energy Scale; LFS, Lee Fatigue Scale; MS, Mean score; MSAS, Memorial Symptom Assessment Scale; NEO-FFI, NEO Five-Factor Inventory; RF, Random Forest

[a]The variable importance score was calculated by the CARET tool (https://topepo.github.io/caret/variable-importance.html) for the random forest model. Variable importance scores are not comparable between models.

Table 5.

Performance of the final models for predicting evening fatigue in the week following the administration of chemotherapy using evening fatigue at time point 1 measured as the scale items of the Lee Fatigue Scale.

Method	Mean Predicted $F2_{Item}$	SD Predicted $F2_{Item}$	Mean RMSE	Relative Performance [a]	2.5% [b]	97.5% [b]
Random Forest	5.61	1.27	1.53	0.0%	1.52	1.54
Linear Regression (Filtered)	5.62	1.53	1.60	4.2%	1.58	1.61
Support Vector Machine	5.69	1.35	1.63	6.5%	1.62	1.64
Linear Regression (Unfiltered)	5.62	1.59	1.64	7.0%	1.62	1.66
RPART	5.62	1.14	1.76	15.3%	1.74	1.79
Mean (null model)	5.62	0.00	2.08	36.0%	2.08	2.09

Abbreviations: CTX, chemotherapy; ELFS, $F2_{Item}$, ELFS total score at time point 2, ELFS total score at time point 2; RMSE, Root mean square error; RPART, Recursive Partitioning and Regression Trees; SD, standard deviation

[a] The ratio of (RSEM model/RSME random forest model) expressed as a percentage.

[b] RMSE percentiles based on simulation (replicate count = 1000).