Prediction of fatigue severity in outpatients one week following administration of chemotherapy (CTX) using accessible data and two short questions

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Introduction

Fatigue is the most common and debilitating symptom experienced by cancer patients undergoing CTX. Prediction of symptom severity can assist clinicians to identify high risk patients and provide education to decrease symptom severity. One major limitation to the implementation of clinically accessible prediction models is commonly available patient data has limited predictive value. Another limitation is the availability of simple to deploy questions for assessing fatigue. Previous studies have identified two questions as strong predictors for fatigue severity. Study purpose was to evaluate performance of predictions of the severity of morning fatigue (AM-F) and evening fatigue (PM-F) using commonly accessible characteristics plus two simple fatigue-specific questions.

Study Sample

Patients and settings

Oncology outpatients (n=1217) who were receiving CTX for breast, lung, gynecological, or gastrointestinal cancers were recruited as part of the previous grant (NCI R01 CA134900) (Figure 1). Patients beginning their 2nd or 3rd cycle of CTX were assessed over two complete CTX treatment cycles (i.e., 6 assessments) using the Lee Fatigue Scale (LFS). In the week prior to their 2nd or 3rd cycle of CTX (i.e., Assessment), patients were asked to rate the severity of CRF in the past week upon awakening (morning) and 30 minutes prior to bedtime (evening).

Instruments

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale, Self-Administered Comorbidity Questionnaire (SCQ), and Alcohol Use Disorders Identification Test (AUDIT). Toxicity of the chemotherapy regimen were rated using the MAX2 index. Medical records were reviewed for disease and treatment information. The 18-item Lee Fatigue Scale (LFS) was used to assess physical fatigue and energy. Each item was rated on a 0 to 10 numeric rating scale. Mean scores were calculated for the 13 fatigue items. Higher scores indicate greater fatigue severity.

Prediction Modeling

Separate prediction models for AM-F and PM-F severity were created using 31 common demographic and clinical patient characteristics and two individual LFS items (i.e., “worn out”, “exhausted”). Characteristics are listed in Table 1 also include lab (eosinophil, lymphocyte, monocyte, neutrophil, platelet, red blood cell, white blood cell, hemoglobin, hemocrit) and demographic (i.e., height and weight) measures. Prediction models were created using two regression and six machine learning (ML) approaches (Figure 2).

Methods

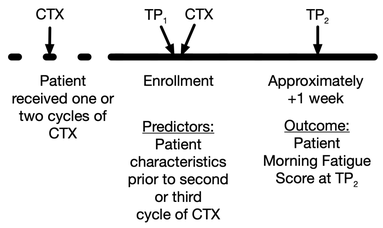

Figure 1. Timeline depicting when the predictor variables at Time Point 1 (TP1) and outcome variable at Time Point 2 (TP2) were collected. All patients were enrolled prior to their second or third cycle of chemotherapy (CTX). TP1 occurred at enrollment into this study and prior to the patient’s second or third cycle of CTX. TP2 occurred approximately one week (+1) after the enrollment visit.

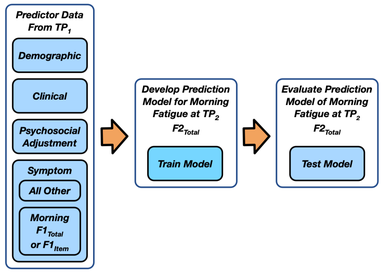

Figure 2. A depiction of the data collected at Time Point 1 (TP1) used to develop the models to predict morning fatigue at Time Point 2 (TP2). Morning fatigue at TP1 is characterized as either the total score (F1 Total) or scale items (F1 Item) of the Lee Fatigue Scale. To avoid bias in prediction error estimates, models were fit utilizing 10-fold cross validations repeated 1000 times. Model performance was measured using mean root mean square error (mRMSE).

Table 1. Demographic, Clinical, Symptom, and Psychosocial Adjustment Characteristics of the Patients at Timepoint 1 in the morning (AM-F) and evening (PM-F) fatigue analyses.

	AM-F (n=1235)	PM-F (n=1217)
Demographic Characteristics		
Age (years; mean (SD))	57 (12.3)	56.9 (12.3)
Gender (% female (n))	78.1 (964)	78 (949)
Ethnicity (% (n))		
White	69.7 (851)	69.6 (836)
Black Non-Hispanic	12.6 (154)	12.8 (154)
Asian/Pacific Islander	6.8 (83)	6.8 (82)
Hispanic/Mixed/Other	10.9 (133)	10.8 (130)
Education (years; mean (SD))	16.2 (3)	16.2 (3)
Married or partnered (% yes (n))	64.1 (779)	63.9 (766)
Lives alone (% yes (n))	21.8 (265)	21.6 (259)
Currently employed (% yes (n))	35.5 (434)	35.2 (425)
Child care responsibilities (% yes (n))	22.5 (273)	22.3 (267)
Income (% (n))		
Less than $30,000		
$30,000 to <$70,000		
$70,000 to < $100,000		
More than $100,000		
Clinical Characteristics		
Self-administered Comorbidity Questionnaire score (mean (SD))	5.4 (3.2)	5.4 (3.2)
Body mass index (kg/m2; mean (SD))	26.2 (5.7)	26.2 (5.7)
Hemoglobin (gm/dL; mean (SD))	11.5 (1.4)	11.5 (1.4)
Karnofsky Performance Status score (mean (SD))	80.2 (12.4)	80.1 (12.5)
Exercise on a regular basis (% yes (n))	71 (858)	70.7 (843)
Cancer diagnosis		
Breast	40.6 (502)	40.8 (496)
Gastrointestinal	30.4 (375)	30.3 (369)
Gynecological	17.4 (215)	17.3 (211)
Lung	11.6 (143)	11.6 (141)
Time since cancer diagnosis (years; mean (SD))	1.9 (3.8)	1.9 (3.8)
Number prior cancer treatments (mean (SD))	1.6 (1.5)	1.6 (1.5)
CTX toxicity MAX2 score (mean (SD))	0.2 (0.1)	0.2 (0.1)
Number of metastatic sites including lymph node (mean (SD))	1.2 (1.2)	1.2 (1.2)
Number of metastatic sites excluding lymph node (mean (SD))	0.8 (1)	0.8 (1.1)
Symptom Characteristics		
Lee Fatigue Scale: evening fatigue total score (mean (SD))	5.3 (2.2)	5.3 (2.1)
Lee Fatigue Scale: morning fatigue total score (mean (SD))	3.1 (2.2)	3.1 (2.3)
Lee Fatigue Scale: evening energy total score (mean (SD))	3.5 (2)	3.5 (2)
Lee Fatigue Scale: morning energy total score (mean (SD))	4.4 (2.3)	4.4 (2.3)

Results

For both AM-F and PM-F, the best performing models using only common data performed similar to the null model (ElasticNet and LASSO, mRMSE delta 0.037 and 0.044, respectively) and models including the two LFS items outperformed the null models (ElasticNet, mRMSE delta 0.275 and 0.281, respectively). Exhaustion and Worn Out variables had the highest importance for both AM-F and PM-F (Table 2) .

Table 2. The top ten predictors with highest variable importance for Elastic Net and LASSO models using accessible variables with and without LFS Scale Items Worn Out and Exhausted variables for (A) morning and (B) evening fatigue at time point 1.

(A)	EN Model Using Accessible variables at T1		EN Model Using Accessible plus LFS Scale Items Worn Out and Exhausted variables at T1	
Rank	T1 Predictor	Score[a]	T1 Predictor	Score[a]
1	Age (years)	100.00	Morning Fatigue $F1_{Item}$ - Worn Out	100.00
2	Income	76.63	Morning Fatigue $F1_{Item}$ - Exhaustion	92.33
3	Exercise on regular basis	57.76	Age (years)	17.49
4	Lives alone	46.54	Income	15.82
5	Body Mass Index	38.37	Neutrophil	11.56
6	Gender	34.66	Exercise on regular basis	9.67
7	Self-reported race	34.01	Gender	8.87
8	Currently employed	32.80	Self-reported race/ethnicity combined measure	8.75
9	Smoker	32.17	Lives alone	8.62
10	Time from cancer diagnosis to start of study (years)	26.66	Eosinophils	8.27

(B)	LASSO Model Using Accessible variables at T1		EN Model Using Accessible plus LFS Scale Items Worn Out and Exhausted variables at T1	
Rank	T1 Predictor	Score[a]	T1 Predictor	Score[a]
1	Age (years)	100.00	Evening Fatigue $F1_{Item}$ - Exhaustion	100.00
2	Self-reported race	98.55	Evening Fatigue $F1_{Item}$ - Worn Out	95.11
3	Gender	53.22	Self-reported race	24.95
4	Income	49.19	Age (years)	18.28
5	Exercise on regular basis	39.49	Has the cancer metastasized to any other sites?	16.75
6	Self-reported ethnicity – Hispanic/Latino	31.66	Self-reported ethnicity – Hispanic/Latino	16.44
7	Smoker	30.83	Red blood cell count	12.42
8	Cancer Diagnosis	26.59	Cancer diagnosis	11.54
9	Has the cancer metastasized to any other sites?	23.04	Exercise on regular basis	10.92
10	Hemocrit	13.98	Income	10.18

Conclusion

First study to evaluate performance of prediction models of AM-F and PM-F severity in the week following CTX from common variables obtained in the week prior to CTX. Models using only common variables were not predictive of fatigue severity. The addition of two simple questions improves prediction of fatigue severity as compared to only commonly available patient data. These findings demonstrate the limitation of currently available characteristics and the potential utility of these two individual items for predicting fatigue severity in a clinical environment.

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