An Evaluation of the Multifactorial Model of Cancer-Related Cognitive Impairment

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Background: Up to 45% of patients report cancer-related cognitive impairment (CRCI). A variety of characteristics are associated with the occurrence and/or severity of CRCI. However, an important gap in knowledge of risk factors for CRCI is the relative contribution of each factor. The multifactorial model of cancer-related cognitive impairment (MMCRCI) is a conceptual model of CRCI that can be used to evaluate the strength of relationships between various factors and CRCI.

Objectives: The purpose of this study was to use structural regression methods to evaluate the MMCRCI using data from a large sample of outpatients receiving chemotherapy (n = 1,343). Specifically, the relationships between self-reported CRCI and four MMCRCI concepts (i.e., social determinants of health, patient-specific factors, treatment factors, and co-occurring symptoms) were examined. The goals were to determine how well the four concepts predicted CRCI and determine the relative contribution of each concept to deficits in perceived cognitive function.

Methods: This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy. Adult patients were diagnosed with breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding 4 weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Self-reported CRCI was assessed using the attentional function index. Available study data were used to define the latent variables.

Results: On average, patients were 57 years of age, college educated, and with a mean Karnofsky Performance Status score of 80. Of the four concepts evaluated, whereas co-occurring symptoms explained the largest amount of variance in CRCI, treatment factors explained the smallest amount of variance. A simultaneous structural regression model that estimated the joint effect of the four exogenous latent variables on the CRCI latent variable was not significant.

Discussion: These findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors, as well as refinements of the model. In terms of risk factors for CRCI, co-occurring symptoms may be more significant than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy.

Key Words: cancer • chemotherapy • cognitive impairment • conceptual model • depression • fatigue • patient-reported outcomes • sleep disturbance • social determinants of health • structural equation model

Nursing Research, July/August 2023, Vol 72, No 4, 272–280

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DOI: 10.1097/NNR.0000000000000660

Cancer-related cognitive impairment (CRCI) is reported by up to 45% of patients (Schmidt et al., 2016). Although not fully understood, the causes of CRCI are thought to be multifactorial (e.g., treatment-related effects, patient-specific characteristics; Bai & Yu, 2021). A variety of cognitive domains are impacted (e.g., memory, attention, processing speed; Ren et al., 2019). Consequently, CRCI negatively impacts the everyday lives of those who experience it (Mayo et al., 2022). Prevention and mitigation strategies for CRCI remain limited (Bai & Yu, 2021), likely because of the lack of understanding of its underlying mechanism(s) and comprehensive evaluation of associated risk factors.

Treatment factors (e.g., hormonal changes, direct effects of chemotherapy) and co-occurring symptoms (e.g., anxiety, depression, fatigue) are among the most frequently identified risk factors for CRCI (Bai & Yu, 2021). In addition, various demographic and clinical characteristics are associated with the

occurrence of CRCI (Janelsins et al., 2017). However, an important gap in our knowledge of the various risk factors is the relative contribution of each risk factor to CRCI. In other words, which risk factor significantly contributes to its occurrence, severity, and/or persistence? This knowledge is needed to begin prioritizing modifiable factors amenable to interventions.

One analytic approach that can be used to explore the strength of the relationships between/among variables is structural regression modeling (i.e., a type of structural equation modeling). Structural regression methods were developed to evaluate complex interrelationship patterns among variables (Maruyama, 1997). Therefore, these methods can be used to estimate the strength of the relationships between variables in a conceptual model (Maruyama, 1997). Using this analytical approach, indicator variables are selected to create an exogenous latent variable representing an otherwise unobserved independent variable (i.e., a hypothetical construct). For example, in the current study, the indicator variables of annual household income, years of education, cumulative lifetime stress, and resilience are used to create an exogenous latent variable that represented "social determinants of health." In contrast, endogenous latent variables represent the dependent or outcome variable (e.g., self-reported CRCI). Although structural regression methods were used to evaluate a number of outcomes in patients with cancer (e.g., posttraumatic growth; (Zhang et al., 2021) and quality of life; (J. L. Lee & Jeong, 2019)), this analytic approach has not been used to evaluate risk factors for CRCI.

The multifactorial model of cancer-related cognitive impairment (MMCRCI) is a comprehensive conceptual model of CRCI that includes factors with known or hypothesized associations with CRCI (Oppegaard et al., 2023). Within the MMCRCI, these factors are organized into broader concepts: social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms, and biologic mechanisms. Although the MMCRCI is based on an extensive review of the literature, it requires testing. Therefore, the purpose of this study was to use structural regression methods to evaluate the MMCRCI using data from a large sample of oncology outpatients receiving chemotherapy. Specifically, the relationships between CRCI and four of the MMCRCI concepts (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms) were examined; the joint effect of the four concepts on CRCI was evaluated; and the unique contribution of co-occurring symptoms on CRCI controlling statistically for the contributions of each of the other three concepts were determined. The overall goal was to verify how well the concepts in the MMCRCI predicted CRCI and determine the relative contribution of each concept to deficits in cognitive function.

METHODS

Study Sample and Procedures

This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy (Miaskowski et al., 2014). In brief, eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding 4 weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two comprehensive cancer centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached, and 1,343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment. Data from the enrollment assessment (i.e., prior to receipt of second or third cycle of chemotherapy) were used in this analysis.

Conceptual Model

The structural regression models (SRMs) evaluated in this study are based on the MMCRCI (Oppegaard et al., 2023). Available study data were used to define observed indicators as latent variables (Kline, 2016) that mapped to each of the concepts in the MMCRCI (Figure 1).

Variables

Demographic questionnaires obtained information on age, gender, ethnicity, education, employment status, and income. Medical records were reviewed for disease and treatment information.

Outcome Variable Self-reported CRCI was assessed using the Attentional Function Index (AFI; Cimprich et al., 2011), a 16-item instrument designed to assess an individual's perceived effectiveness in performing daily activities that are supported by attention, working memory, and executive functions (e.g., setting goals, planning, and carrying out tasks). A higher total mean score on a 0–10 numeric rating scale indicates greater capacity to direct attention (Cimprich et al., 2011). Clinically useful cut points for attentional function are as follows: <5.0, low function; 5.0–7.5, moderate function; and >7.5, high function (Cimprich et al., 2005). Cronbach's alpha for the total AFI score was .93.

Latent Variables Estimation of the endogenous latent CRCI variable was carried out with a measurement model that used the individual AFI items as indicators of the latent score. When that measurement model was examined, because numerous correlated residuals were found among the items, the fit of the measurement model to the data was very poor. Therefore, the latent CRCI score was estimated following the recommendations of Jøreskog and Sørbom (as reported in (Raykov & Marcoulides, 2006) by estimating the measurement error and residual variance as (1 − reliability) × AFI computed variance. This value was defined as the CRCI "latent variable" residual variance for the subsequent SRMs.

Measurement models for each exogenous latent variable were created using MMCRCI concepts (i.e., social determinants

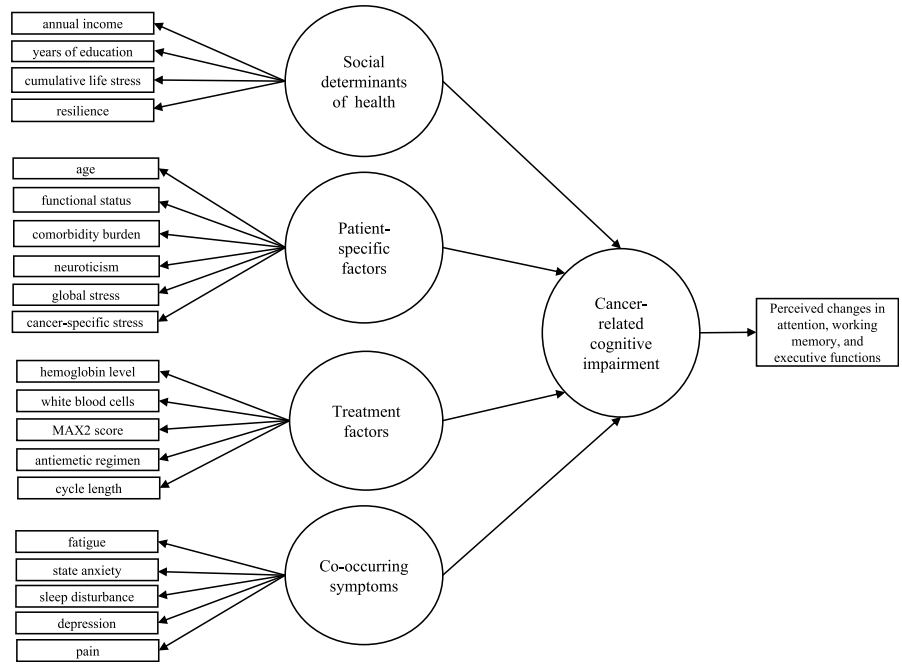

FIGURE 1. The hypothetical model to be evaluated based on the Multifactorial Model of Cancer-Related Cognitive Impairment.

of health, patient-specific factors, treatment factors, co-occurring symptoms). The indicator variables for each exogenous latent variable were selected from available study data. Specific information about each exogenous latent variable is described below (see Figure 1).

Social Determinants of Health

Indicator variables used for this exogenous latent variable included annual household income, years of education, cumulative lifetime stress, and resilience. Cumulative lifetime stress was assessed using the Life Stressor Checklist–Revised, an index of lifetime trauma exposure (e.g., being mugged, death of a loved one, sexual assault; Wolfe & Kimerling, 1997). Resilience was assessed using the Connor–Davidson Resilience Scale, an instrument that evaluates a patient's personal ability to handle adversity (Connor & Davidson, 2003).

Patient-Specific Factors

Indicator variables for this exogenous latent variable included age, functional status, comorbidity burden, the personality domain of neuroticism, global perceived stress, and cancer-specific stress. Functional status was assessed using the Karnofsky Performance Status (KPS) Scale (Karnofsky et al., 1948). Comorbidity burden was assessed using the Self-Administered Comorbidity Questionnaire score (Sangha et al., 2003). The personality domain of neuroticism was assessed using the NEO Five-Factor Inventory (NEO-FFI; Costa & McCrae, 1992). Global perceived stress was assessed using the Perceived Stress Scale (Cohen et al., 1983), a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week. Cancer-specific stress was assessed using the Impact of Event Scale–Revised (Weiss & Marmar, 1997).

Treatment Factors

Indicator variables for this exogenous latent variable included hemoglobin level, white blood cell count, toxicity of chemotherapy regimen, antiemetic regimen (i.e., number and type[s] of antiemetic medications), and chemotherapy cycle length. The toxicity of the chemotherapy regimen was determined using the MAX2 index (Extermann et al., 2004). Briefly, the MAX2 score is the average of the most frequent Grade 4 hematologic toxicity and the most frequent Grades 3–4 nonhematologic toxicity reported in publications of a regimen; it correlates well with that regimen's average overall risk of severe toxicity.

Co-occurring Symptoms

Indicator variables for this exogenous latent variable included severity of morning and evening fatigue, state anxiety, sleep disturbance, depressive symptoms, and severity of worst pain. The Lee Fatigue Scale (K. A. Lee et al., 1991) assessed morning and evening fatigue. State anxiety was assessed using the Spielberger State Anxiety Inventory (Spielberger et al., 1983). Sleep disturbance was assessed using the General Sleep Disturbance Scale (K. A. Lee, 1992). Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (Radloff, 1977). Severity of worst pain was assessed using the Brief Pain Inventory (Daut et al., 1983).

Statistical Analysis

Statistical analyses were performed with Stata Version 16.1 (StataCorp, College Station, TX). Means, standard deviations,

and percentages were calculated for demographic and clinical characteristics. All variables were assessed for appropriateness for inclusion in the SRMs. Indicator variables that were included in the models were either continuous or ordinal. Given the large sample size, normality of the parameter estimates was assumed based on the central limit theorem (Kwak & Kim, 2017). Missing data were accommodated with the use of full information maximum likelihood and the expectation–maximization algorithm (Muthén & Shedden, 1999). In Stata, this method of estimation is called maximum likelihood with missing values (mlmv).

Most of the models employed the usual Newton–Raphson (NR) algorithm for likelihood estimation. However, convergence with NR failed for the most complex models when mlmv was used. For these models, the Berndt–Hall–Hall–Hausman (BHHH) algorithm was used for several (e.g., 10) iterations, then estimation switched to NR for several iterations, then back to BHHH until convergence was achieved. Model fit for each measurement model and SRMs was evaluated using recommended fit indices. Absolute fit was evaluated using the chi-square test of goodness of fit (Kline, 2016). Model parsimony was evaluated using the root-mean-square error of approximation (RMSEA; Browne & Cudeck, 1992). Comparative fit was evaluated using the comparative fit index (CFI; Bentler, 1990). A chi-square close to nonsignificant, RMSEA of <.06, and CFI of >.95 were used as the desirable cut points for these fit indices.

Modification indices were examined to improve model fit by incorporating correlated residuals into some measurement models for exogenous latent variables. Standardized parameter estimates for the measurement model coefficients were used to interpret the relative importance of indicators measured on incongruent scales. A two-sided *p*-value of <.05 was considered statistically significant for hypothesis tests on the unstandardized coefficients. SRMs were built in the following order: an individual measurement model for each exogenous latent variable was estimated with significant coefficients, an individual SRM for the CRCI latent variable was regressed on each exogenous latent variable, and a simultaneous SRM was evaluated that regressed the CRCI latent variable on the four exogenous latent variables jointly. Finally, three hierarchical SRM were built to estimate the unique contribution of co-occurring symptoms on the CRCI latent variable, controlling for either the effect of social determinants of health, patient-specific factors, or treatment factors.

RESULTS

Sample Characteristics

Demographic, clinical, symptom, stress, and resilience characteristics of the 1,343 patients are summarized in Table 1. On average, patients were 57 years of age and college educated, with a mean KPS score of 80. The majority were female, White, receiving only chemotherapy, and receiving chemotherapy on a 21-day cycle. Patients in this study had an average AFI score of 6.4, which suggests a moderate level of CRCI.

Measurement Models for Each Exogenous Latent Variable

Fit indices for the measurement models for each exogenous latent variables are listed in Table 2. All models' fit indices met the established cut points (i.e., chi-square close to nonsignificant, RMSEA of <.06, and CFI of >.95). Details on each measurement model for the four exogenous latent variables are provided in Appendix A, http://links.lww.com/NRES/A468.

SRM for the CRCI Latent Variable Regressed on Each Exogenous Latent Variable

Results of the individual SRM for the CRCI latent variable regressed on each of the exogenous latent variables are listed in Table 3. As indicated by the standardized path coefficients, co-occurring symptoms (−0.762), patient-specific factors (−0.658), and social determinants of health (0.653) had the largest effects on the CRCI latent variable. In contrast, treatment factors (0.092) had the smallest effect. Details on each of the SRM for the CRCI latent variable regressed on each exogenous latent variable are provided in Appendix A, http://links.lww.com/NRES/A468.

Simultaneous and Hierarchical SRM

A simultaneous SRM that estimated the joint effect of the four exogenous latent variables on the CRCI latent variable was not significant (data not shown). The results of each hierarchical SRM that estimated the effect of co-occurring symptoms on the CRCI latent variable, controlling for each exogenous latent variable, are listed in Table 4. For each SRM, pairwise comparisons were done that evaluated the unique contribution of co-occurring symptoms using the difference in R^2 between a model for one of the other three exogenous variables alone, followed by a model with co-occurring symptoms added. The unique variance contributions of co-occurring symptoms on CRCI, after controlling for social determinants of health, patient-specific factors, or treatment factors, were 0.203, 0.144, and 0.574, respectively.

DISCUSSION

In a large sample of patients receiving chemotherapy, this study is the first to use structural regression methods to examine the relationships between self-reported CRCI and four of the concepts in the MMCRCI (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms). Specifically, CRCI was operationalized as perceived changes in the domains of attention, working memory, and executive functions as measured by the AFI. This evaluation included an examination of the joint effect of the four concepts on predicting CRCI. In addition, in three separate SRMs,

TABLE 1. Demographic, Clinical, Stress, Resilience, and Symptom Characteristics (n = 1,343)

Demographic and clinical characteristics	Mean (*SD*)
Age (years)	57.2 (12.4)
Education (years)	16.2 (3.0)
Neuroticism personality domain	15.1 (8.0)
Karnofsky Performance Status score	80.0 (12.5)
Self-administered Comorbidity Questionnaire score	5.5 (3.2)
MAX2 score	0.17 (0.08)
Hemoglobin	11.5 (1.4)
White blood cell count	7.3 (4.1)
	% (*n*)
Gender (% female)	77.8 (1044)
Self-reported ethnicity	
American Indian/Alaskan Native	0.46 (6)
Asian	11.8 (155)
Black or African American	7.5 (98)
Native Hawaiian or other Pacific Islander	1.0 (13)
White	72.9 (956)
Mixed ethnic background	5.3 (69)
Other	1.1 (15)
Annual household income	
Less than $30,000	18.4 (221)
$30,000 to $70,000	21.2 (254)
$70,000 to $100,000	16.9 (203)
Greater than $100,000	43.6 (523)
Cancer diagnosis	
Breast cancer	40.2 (540)
Gastrointestinal cancer	30.7 (412)
Gynecological cancer	17.4 (233)
Lung cancer	11.8 (158)
CTX regimen	
Only chemotherapy	70.1 (922)
Only targeted therapy	3.0 (39)
Both chemotherapy and targeted therapy	26.9 (354)
Cycle length	
14-day cycle	42.1 (558)
21-day cycle	50.6 (671)
28-day cycle	7.3 (97)
Antiemetic regimen	
None	7.1 (92)
Steroid alone or serotonin receptor antagonist alone	20.5 (265)
Serotonin receptor antagonist and steroid	47.7 (618)
Neurokinin-1 receptor antagonist and two other antiemetics	24.8 (321)
Stress and resilience measures[a]	**Mean (*SD*)**
Perceived Stress Scale total score	18.5 (8.2)
Impact of Event Scale–Revised total score (≥24)	18.8 (13.1)
Life Stressor Checklist–Revised total score (range: 0–30)	6.1 (3.9)
Connor–Davidson Resilience Scale total score (range: 0–40)	30.1 (6.4)
Symptoms[a]	
Depressive symptoms (≥16.0)	12.8 (9.7)
State anxiety (≥32.2)	33.9 (12.4)
Morning fatigue (≥3.2)	3.5 (2.9)
Evening fatigue (≥5.6)	5.9 (2.7)
Sleep disturbance (≥43.0)	52.5 (20.2)
Attentional function (<5.0 = low, 5–7.5 = moderate, >7.5 = high)	6.4 (1.8)
Worst pain intensity score (range: 0–10)	6.1 (2.5)

Note. SD = standard deviation.
[a]Clinically meaningful cutoff scores or range of scores are in parentheses.

the unique contribution of co-occurring symptoms on CRCI was estimated after controlling for each of the other concepts.

A strength of this study is the evaluation of the unobservable influence of the broader MMCRCI concepts on CRCI through the creation of exogenous latent variables. Good model fit was achieved for each of the measurement models that represented the MMCRCI concepts (i.e., the exogenous latent variables; Table 2). As noted in one review (Ahles & Hurria, 2018), specific groups of risk factors, rather than individual risk factors, may increase patients' risk for CRCI. Our results support this hypothesis and provide initial information on groups of risk factors that warrant further evaluation.

Each exogenous latent variable was significantly associated with the CRCI latent variable. These findings suggest that these four MMCRCI concepts are valid predictors of CRCI and support the multifactorial nature of CRCI. Most of the indicator variables selected for each exogenous latent variable were supported by available evidence (Oppegaard et al., 2023). However, some of the indicator variables are relatively novel. For example, some personality domains (e.g., neuroticism, openness) are associated with an increased risk for other types of cognitive impairment (Curtis et al., 2015). However, in the only study of patients with cancer (Hermelink et al., 2010), negative affectivity was associated with decrements in self-reported cognition and attention. The specific domain of neuroticism from the NEO-FFI was selected as one of the indicator variables in the patient-specific latent variable because of its association with CRCI in our sample. However, other personality domains warrant evaluation in future studies.

In terms of other novel indicator variables, cumulative life stress and resilience were included as part of the social determinants of health latent variable. Cumulative life stress was included because it is associated with other social determinants

TABLE 2. Fit Indices for the Measurement Models for Each Exogenous Latent Variable

Latent variable	Chi-square (*df*)	*p*	RMSEA	CFI
Social determinants of health	6.35 (2)	.042	.040	.982
Patient-specific factors	21.78 (7)	.003	.040	.992
Treatment factors	6.97 (3)	073	.031	.986
Co-occurring symptoms	22.61 (7)	.002	.041	.994

Note. CFI = comparative fit index; *df* = degrees of freedom; RMSEA = root-mean-square error of approximation.

TABLE 3. Results of Individual Structural Regression Models for the Cancer-Related Cognitive Impairment Latent Variable Regressed on Each of the Exogenous Latent Variables

Exogenous latent variable	*p*	Path coefficient	Standardized path coefficient	Model R^2
Social determinants of health	.001	0.863	0.653	.427
Patient-specific factors	< .001	–0.873	–0.658	.433
Treatment factors	.028	0.092	0.092	.008
Co-occurring symptoms	< .001	–1.177	–0.762	.581

of health (e.g., lower income, discrimination; Mikhail et al., 2018). In terms of resilience, as noted in one review (Lopez et al., 2021), individuals vary considerably in their ability to adapt to various life stressors, as well as in the development of resilience. Therefore, resilience is an important factor to consider as part of a more comprehensive evaluation of cumulative life stress and other social determinants of health. It is worth noting that resilience was included in the patient-specific factors concept in the original MMCRCI. However, the authors describe potential overlap among the model concepts, which supports the inclusion and evaluation of resilience as part of the social determinants of health latent variable.

Annual income and years of education were the other indicator variables included in the social determinants of health latent variable. In a study that evaluated associations between formal education, income, and cognitive function across 22 countries with varying income levels (Rodriguez et al., 2021), findings suggest that education had the dominant effect on cognitive functioning. Of note, this effect was large enough that it may offset the adverse impact of living in poverty on cognitive function. Although the current study evaluated one set of factors to represent the concept of "social determinants of health," additional research is warranted to determine which social determinants are the most significant risk factors for CRCI.

In terms of the other types of stress, indicator variables representing global and cancer-specific stress were included in the patient-specific factors latent variable. As Ahles and Hurria (2018) noted, studies are needed to evaluate stress as a risk factor for CRCI. Although this study aimed not to examine the effect of the individual indicator variables, global stress was the variable within the patient-specific factors' latent variable that had the largest association with CRCI (Appendix A, http://links.lww.com/NRES/A468). This finding is consistent

TABLE 4. Hierarchical Structural Regression Models That Estimate Unique Contribution of Co-occurring Symptoms on the Cancer-Related Cognitive Impairment Latent Variable for Either Social Determinants of Health, Patient-Specific Factors, or Treatment Factors

Exogenous latent variables	Models	Path coefficient	*Z*-statistic	*p*	Model R^2	Change in R^{2a}	95% Confidence interval
Pairwise comparison model testing for social determinants of health							
SDOH[b]	Model 1	0.863	8.27	<.001	.427	n/a	[0.66, 1.07]
SDOH	Model 2	0.443	3.37	.001	.630	.203	[0.19, 0.70]
CoOccSym[c]		–0.951	–9.11	<.001			[–1.16, –0.75]
Pairwise comparison model testing for patient-specific factors							
PtSpecFx[d]	Model 1	–0.873	–19.50	<.001	.433	n/a	[–0.96, –0.79]
PtSpecFx	Model 2	0.611	1.92	.055	.577	.144	[–0.01, 1.23]
CoOccSym		–1.729	–4.92	<.001			[–2.42, –1.04]
Pairwise comparison model testing for treatment factors							
TxFx[e]	Model 1	0.092	2.20	.028	.008	n/a	[0.01, 0.17]
TxFx	Model 2	–0.059	–1.18	.237	.582	.574	[–0.16, 0.04]
CoOccSym		–1.189	–18.23	<.001			[–1.32, –1.06]

Note. SDOH = social determinants of health; CoOccSym = co-occurring symptoms; PtSpecFx = patient specific factors; TxFx = treatment factors; SRM = structural regression model.

[a]Change in R^2 between SRM of latent variable and outcome variable versus SRM of latent variable, outcome variable, and co-occurring symptoms.

[b]Indicator variables for social determinants of health included years of education, annual income, cumulative lifetime stress, and resilience levels.

[c]Indicator variables for co-occurring symptoms included morning and evening fatigue, state anxiety, depressive symptoms, sleep disturbance, and occurrence of pain.

[d]Indicator variables for patient-specific factors included age, functional status, comorbidity burden, the personality domain of neuroticism, perceived stress, and cancer-specific stress.

[e]Indicator variables for treatment factors included white blood cell count, hemoglobin level, a rating of the toxicity of the chemotherapy regimen, number and type(s) of medications in the antiemetic regimen, and chemotherapy cycle length.

with previous research that found that higher levels of perceived stress were an independent predictor for self-reported CRCI (Kim & Abraham, 2021). In addition, this finding supports the need to evaluate various types of stress as risk factors for CRCI.

Interestingly, the simultaneous SRM that evaluated the joint effect of the latent variables that represented the four MMCRCI concepts on CRCI was not significant. This finding was unexpected for two reasons. First, each exogenous latent variable was independently and significantly associated with the CRCI latent variable. Second, based on conservative estimates of observations to predictor ratios for SRM (e.g., 15:1), the large sample size in the current study allowed for evaluation of a complex SRM (Babyak, 2004). However, it is possible that the level of multicollinearity among the variables and/or small effect sizes contributed to this result (Babyak, 2004). Taken together, the joint effect of the four MMCRCI concepts may be difficult to parse out when evaluated in a complex SRM despite an adequate sample size. Rather than a complex SRM, future studies using the MMCRCI can test smaller and/or individual parts of the model.

Of the four MMCRCI concepts evaluated, treatment factors explained the smallest amount of variance in CRCI. Data on a relatively comprehensive list of treatment-related factors (i.e., white blood cell count, hemoglobin level, a rating of the toxicity of the chemotherapy regimen, number and type[s] of medications in the antiemetic regimen, chemotherapy cycle length) were included in this exogenous latent variable. This finding supports previous research that found that CRCI occurs independent of treatment factors (e.g., it happens prior to treatment; (Bai & Yu, 2021), months to years after completion of treatment; (Lv et al., 2020), across various cancer types; (Vannorsdall, 2017), and independent of treatment regimen; (Janelsins et al., 2017)). Although not evaluated routinely, the inclusion of the type of antiemetic regimen was justified because of the potential adverse effects associated with these medications (e.g., mood changes, fatigue) that may impact cognitive function (Adel, 2017). However, some treatment factors that were not included in this exogenous latent variable but were associated with CRCI, for example, dose intensity (Bai & Yu, 2021) and higher number of chemotherapy cycles (Hodgson et al., 2013), need to be evaluated in future studies of the MMCRCI.

In contrast, co-occurring symptoms explained the largest amount of variance in CRCI (Table 4). This exogenous latent variable included some of the most common symptoms associated with cancer and its treatments (i.e., morning and evening fatigue, state anxiety, sleep disturbance, depression, pain; Miaskowski et al., 2014). Our findings are consistent with previous research that found that decrements in cognitive function were associated with each of these co-occurring symptoms (e.g., fatigue (Abd-Elfattah et al., 2015), anxiety (Smith et al., 2021), sleep disturbance (Song et al., 2021), depression (Rock et al., 2014), and pain (Zis et al., 2017)).

In addition, the hierarchical regression models demonstrated the unique contribution of co-occurring symptoms on CRCI even after controlling for social determinants of health, patient-specific factors, and treatment factors (Table 4). Across these three models, co-occurring symptoms accounted for a large amount of variance in CRCI. These findings showcase several critical directions for future research. First, common mechanism(s) may be driving multiple co-occurring symptoms in patients with cancer. Importantly, research that focuses on identifying common mechanism(s) for co-occurring symptoms is sparse (Harris et al., 2022). Second, future studies need to consider evaluating other common symptoms that co-occur with CRCI. As noted by Lacourt et al. (2018), a need exists to identify different phenotypes of CRCI based on the presence of other co-occurring symptoms. Finally, our findings support previous research that suggests that intervention strategies that can effectively target more than one symptom may significantly improve cognitive function (Vega et al., 2022).

Although this study has numerous strengths (e.g., the first study to evaluate the MMCRCI, use of a large sample of patients receiving chemotherapy, and inclusion of a variety of factors known or hypothesized to be associated with CRCI), some limitations are worth noting. First, operationalizing the concepts and outcomes for evaluating the MMCRCI were limited to the available data and/or appropriateness for use in SRM. Other indicator variables can be used to define and test this model and may yield different findings. For example, testing this model based on an objective measure of CRCI may provide different insights into the relationships between/among the various concepts in the MMCRCI. In addition, because other potentially important risk factors for CRCI (e.g., gender, type of cancer) were represented by nominal variables in this study, they could not be evaluated as part of a latent variable. Finally, these data represent one time point in the treatment trajectory. Longitudinal evaluation of these findings is warranted in future studies.

Conclusion

Our findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as refinements of the model. In terms of risk factors for CRCI, co-occurring symptoms may be more important than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy. This knowledge can be used to design future studies as well as prioritize interventions to prevent and/or improve CRCI.

Accepted for publication December 19, 2022.

This study was funded by a grant from the National Cancer Institute (CA134900). Ms. Oppegaard was supported by a grant from the National Institute of Nursing Research (T32NR016920) and the Oncology Nursing Foundation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Miaskowski is an American Cancer Society clinical research professor.

The study was approved by the Committee on Human Research at the University of California San Francisco and the institutional review boards at each study site. All patients gave written informed consent.

The authors have no conflicts of interest to report.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.nursingresearchonline.com).

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