Causal Cascade of Symptoms on Patient Functioning and Health-Related Quality of Life in Non–Small Cell Lung Cancer and Metastatic Breast Cancer

Donald E. Stull, PhD[1]

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ABSTRACT

PURPOSE Health-related quality of life (HRQoL) is a valuable counterpart to other end points in oncology trials. However, when analyzing the effect of treatment on HRQoL, results are often mixed. Cancer and its treatment can have direct and indirect effects on symptoms such as pain, nausea, and fatigue. These, in turn, can affect the patients' physical and social functioning and ultimately their HRQoL. This causal cascade requires methodologies, such as structural equation modeling, to estimate direct, indirect, and total effects of symptoms on more distal HRQoL outcomes.

METHODS Data were obtained from two multicenter, randomized trials available from Project Data Sphere, LLC. One trial included patients with non–small cell lung cancer; the other included patients with metastatic breast cancer. Structural equation models were evaluated; models included symptom items from the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire, QLQ-C30 (version 3). A causal cascade of individual symptoms at two time points was hypothesized to affect fatigue, which, in turn, had direct and indirect effects on the functional and HRQoL measures.

RESULTS Results showed a logical, causal ordering among EORTC QLQ-C30 outcomes. In the final model, the effects of most symptoms on functional domains and the quality of life (QoL) scale were through their direct effect on fatigue, which, in turn, affected patient functioning and HRQoL.

CONCLUSION Results strongly suggest that when examining the effects of symptoms on EORTC QLQ-C30 functional scales or HRQoL, symptoms would generally not show direct effects on these more distal outcomes. The results from the two clinical trials demonstrated that anticipating a causal cascade from specific symptoms to functional domains and HRQoL would yield more meaningful results.

ACCOMPANYING CONTENT

Data Sharing Statement

Protocol

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INTRODUCTION

Patient-reported outcomes in oncology trials provide a unique, patient-centered perspective of the disease and its treatment beyond overall survival or progression-free survival (PFS).[1] The value of patient-reported health-related quality of life (HRQoL) may be particularly important given that many patients are diagnosed with advanced stages of cancer and treatment has limited effects on survival. Thus, a focus on maintaining a patient's HRQoL under these circumstances becomes a key goal in the treatment plan.[2]

Examining the effects of disease- or treatment-related symptoms on patient functioning or HRQoL requires thinking about how these are related via a causal cascade.[3,4] That is, many symptoms will not have direct effects on different domains of functioning (eg, physical or social functioning) or HRQoL. In fact, some symptoms (eg, pain) will affect other symptoms (eg, fatigue), and both will likely affect functioning and HRQoL. Thus, irrespective of a specific treatment, if a patient experiences pain, resulting from tumor enlargement, or nausea and vomiting, resulting from treatment, they might have a downstream effect on HRQoL and some of their effects will be indirect. The purpose of this study is to examine this causal cascade of direct and indirect relationships among symptoms, functioning, and HRQoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in two clinical trials: one for non–small cell lung cancer (NSCLC) and the other for metastatic breast cancer (mBC).

This can help researchers anticipate that some direct relationships will be null, yet their indirect effects may be significant and meaningful.

THE CAUSAL CASCADE

Many phenomena in clinical and health outcome research involve causal cascading pathways. For example, an increase in tumor size can increase pain, which can increase fatigue, and this can reduce physical functioning, ultimately leading to a reduction in HRQoL.[3,5] Thus, pain has a downstream and indirect effect on HRQoL. Furthermore, if treatment sufficiently shrinks tumor size, thus reducing pain, the effects can cascade to have the indirect effect of improving HRQoL. A focus on the direct effect of treatment on more distal outcomes, such as functioning or HRQoL, may result in an underestimate of its effect because of the more complex causal pathways involved (ie, indirect/mediated pathways).[3,4] The effect of treatment on pain, pain on fatigue, and pain and fatigue on physical functioning and the effects of all these on HRQoL would need to be considered to capture the full effect of treatment on HRQoL, not just the direct effect.

Appropriate estimation of this causal cascade requires explicit specification of causal hypotheses and corresponding analyses to test those hypotheses. An analytic framework must be used that can explicitly model direct, indirect/mediated, and total effects[6] between these variables to provide empirical support that not only symptoms themselves may be causally related (eg, greater pain results in greater fatigue) but also these symptoms have downstream effects on functioning and HRQoL.

To avoid this potential underestimation of the effects of treatment or symptoms on patient experience, a full conceptual model should be developed based on existing research and informed by clinical expertise and patient input that can be tested using structural equation modeling (SEM). Methods such as SEM have been used to examine causal cascades in data from randomized controlled trials (RCTs) and observational studies.[7-9] Bollen and Pearl[10] argued that the capability of SEM to formally and explicitly hypothesize and test causal inferences is extremely robust and indispensable. There are examples of using the SEM approach to develop or test conceptual models and the underlying factor structure of the EORTC QLQ-C30 as outcome measures for oncology studies.[11,12] However, these analytic methods have not been used routinely to examine and quantify the direct, indirect, and total effects of patient-reported symptoms on functioning and HRQoL when evaluating oncology trial data.

The objective of the present analyses was to provide support that a causal cascade of effects from symptoms to patient functioning to HRQoL is evident in patients being treated for two different types of cancers—NSCLC and mBC—and that the causal cascade is similar for patients undergoing treatment for either type of cancer. Furthermore, a key goal was to demonstrate that while a direct relationship between symptoms and HRQoL might not have empirical support, there may be a statistically significant *indirect* relationship.

METHODS

Data

Data were obtained from two trials available from Project Data Sphere, LLC. In general, the trials available from Project Data Sphere, LLC, include only the comparator arm. For the purpose of the present analyses, there is no interest in comparing efficacy of treatments in the EORTC QLQ-C30. Our interest is in demonstrating that there is a causal cascade among the symptoms, functional domains, and overall HRQoL. Consequently, having data from only the comparator arm does not affect this goal.

The first trial uses data from an AstraZeneca Phase III randomized, double-blind, multicenter parallel-group trial to assess the effect of ZD6474 (vandetanib/ZACTIMA) versus erlotinib (TARCEVA) in patients with locally advanced or metastatic (stage IIIB to IV) NSCLC after failure of at least one previous cytotoxic chemotherapy (ClinicalTrials.gov identifier: NCT00364351). Patients were randomly assigned 1:1 to receive either ZD6474 or erlotinib as a once-daily oral dose. The goal of the trial was to investigate whether vandetanib (300 mg/d) prolonged PFS compared with erlotinib monotherapy (150 mg/d) in a once-daily dose in patients with previously treated advanced NSCLC.[13] The data used for the present analyses were from the erlotinib arm at baseline and week 4 (N = 438 at baseline).

The second trial uses data from an American BioSciences, Inc.–sponsored controlled randomized, phase III, multicenter, open-label study of ABI-007 (a Cremophor-free, protein-stabilized, nanoparticle Paclitaxel) and TAXOL in patients with mBC (ClinicalTrials.gov identifier: NCT00046527). Patients were randomly assigned 1:1 to receive either ABI-007 (260 mg/m^2) or TAXOL (175 mg/m^2) on an outpatient basis for a maximum of six cycles. This phase III study was performed to confirm preclinical studies demonstrating superior efficacy and reduced toxicity of ABI-007 compared with standard paclitaxel.[14] The data for these analyses were from the TAXOL arm at baseline and week 6 (cycle 3) of treatment (N = 224 at baseline).

Measure

The primary measure used in the present analyses for both trials was the EORTC QLQ-C30 Version 3.[15] The QLQ-C30 is a validated and reliable disease-specific PRO questionnaire developed to assess HRQoL of patients with cancer. It consists of 30 items assessing three main dimensions: global health status/quality of life (GHS/QoL; two items); patient functioning scales (15 items assessing five functional domains: physical [five items], role [two items], emotional [four items], social [two items], and cognitive functioning

[two items]); three multi-item symptom scales (fatigue [three items], pain [two items], and nausea plus vomiting [two items]); and five single-item symptom measures to assess dyspnea, insomnia, appetite loss, constipation, and diarrhea; and one item assessing financial difficulties of disease. A linear transformation of the scales and single-item measures are recommended, with scores ranging from 0 to 100, reflecting increasingly higher states of functioning or quality of life or increasingly higher symptom levels. In the present analyses, all multi-item scales were converted to composite scores ranging from 0 to 100.

Analytic Methods

The main analysis was SEM of the QLQ-C30 data to evaluate the effect of symptoms on other symptoms, the functional domains, and the two-item GHS/QoL domain. In line with previous research,[3,4] it was hypothesized that there is a causal cascade among the symptoms, functional domains, and GHS/QoL, such that some symptoms would be antecedent to others (eg, nausea, vomiting, pain, and dyspnea would precede fatigue) and some symptoms would precede the functional domains and GHS/QoL.

The path analytic underpinnings of SEM were used to decompose correlations between two variables into direct and indirect (sometimes called mediating) effects to better understand the network of relationships between the variables of the QLQ-C30. For example, a correlation between pain and physical functioning would be composed of a direct path between these two variables and an indirect path involving the effect of pain on fatigue and the effect of fatigue on physical functioning. If the combination of these two paths does not equal the correlation between pain and physical functioning, we have evidence that our proposed model is incorrect (ie, one or more paths were not included in the analysis). For more information on the process of identifying and tracing indirect paths, see the study by Asher.[16]

One of the many strengths of SEM is the ability to evaluate a full hypothetical model in a single analysis, rather than in a piecewise fashion as when using regression-based path analysis, and to obtain measures of fit of the hypothesized model to the data. Thus, competing or alternative models can be compared in terms of model fit to help make decisions about which model fits the data best. In addition, modification indices are available which give clues about misfit between the model and the data or where improvement in model fit would occur if specific paths that are hypothesized to be zero (ie, no relationship) are allowed to be nonzero.

All SEM analyses were conducted using Mplus version 8.6.[17] Model chi-square results were estimated to assess the model fit to the data or to tentatively reject the model and interpret the approximate fit indices. The values of a key set of fit indices are presented, including root mean square error of approximation (RMSEA) plus the 90% CI, comparative fit index (CFI), and standardized root mean square residual (SRMR).[18]

Hypothesized Model

Identical, preliminary models for both trials were analyzed, and small adjustments were made based on modification indices. The initial hypothesized model of the relationships among symptoms, functional domains, and GHS/QoL, which was the basis for all analyses, is shown in Figure 1. Note that the figure contains boxes that represent the manifest (ie,

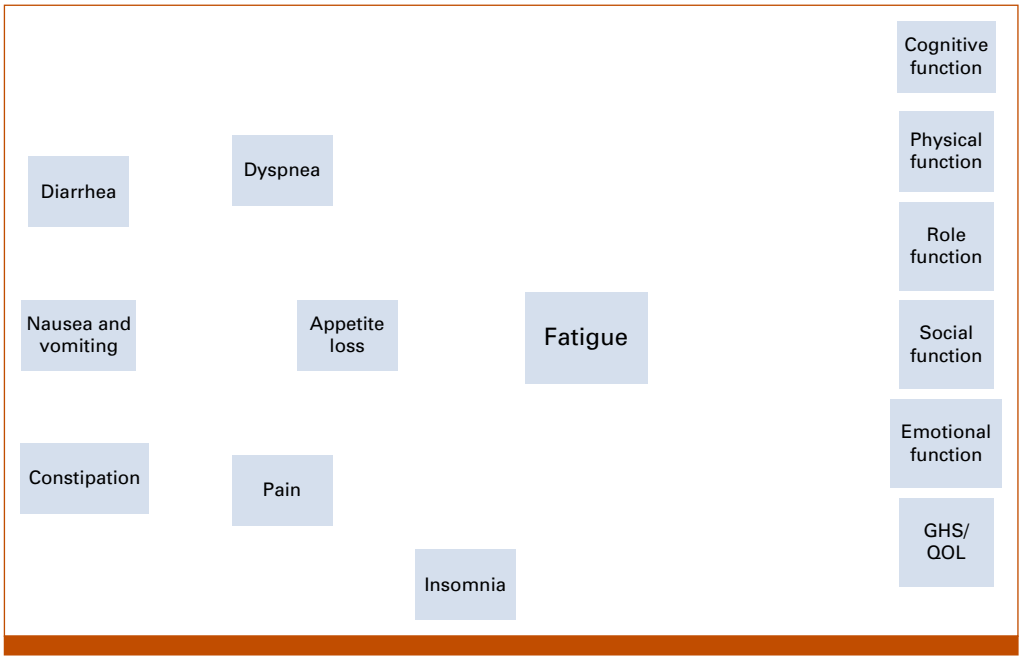


FIG 1. Initial hypothetical model. GHS/QoL, global health status/quality of life.

observed) variables of the symptoms, functional domains, and GHS/QoL. That is, there is no measurement model included in these analyses to minimize loss of degrees of freedom. Thus, this model focuses on the structural paths linking the various variables. Moreover, this uses the multi-item domains (eg, nausea and vomiting, fatigue, functional domains, and GHS/QoL) as composite scores, the typical way in which they are used in the literature. The symptoms, functional domains, and GHS/QoL were used as described in the QLQ-C30 Version 3 scoring manual, so they are consistent with what is generally shown in the literature.

This preliminary model was informed by previous work in oncology, which used data from trials in NSCLC and mBC.[3-5] This model does not include causal paths or covariances/correlations between symptoms, functional domains, and GHS/QoL to simplify the presentation; otherwise, it would have so many paths that it would be difficult to identify the individual relationships. Instead, when boxes, representing symptoms or functional domains, are in vertical alignment, those variables are hypothesized to be correlated and occur contemporaneously. For example, diarrhea, nausea and vomiting, and constipation are correlated. There is no a priori justification for hypothesizing a causal relationship among these symptoms. Similarly, the functional domains and GHS/QoL are all hypothesized as being correlated. When a box/manifest variable is to the right of another, it is hypothesized that the variable to the left is antecedent to the one to its right. For example, fatigue is likely due to the amount of pain or the degree of dyspnea (shortness of breath) that a patient experiences.

With SEM, it is critical that the hypothesized model is prespecified. In this way, the analyst is comparing their hypothesized model (ie, how they think the variables are related to one another) with the actual data, thereby obtaining measures of fit between the hypothesized model and the actual data. This process is thus confirmatory rather than exploratory. Each nonzero path is explicitly specified in the software allowing for a test of its correctness (ie, is it truly nonzero?) and the strength of the relationship. Similarly, paths that are thought to be zero (ie, no relationship) are implicitly built into the model and modification indices show whether that assumption is correct.

"Financial difficulties associated with their condition or treatment" was not included in the present analytic model since it was considered peripheral to the symptoms and HRQoL domains in the full instrument. Furthermore, this item is often not reported in the published literature.[12]

RESULTS

Initial analyses at both time points in both trials suggested some slight modifications to the original hypothetical model of the causal cascade of the QLQ-C30. A change in the model for one trial was matched for the other trial to keep the hypothesized models identical for each trial to evaluate the extent to which a common model explains the relationships among symptoms, functional domains, and GHS/QoL for both types of cancers. For example, modification indices in at least one trial suggested that the addition of correlations between dyspnea and pain and between cognitive functioning and physical, role, emotional, and social functioning would improve model fit. In addition, a correlation between constipation and pain significantly improved model fit. It should be noted that adding correlations (or correlated errors) simply to improve model fit is strongly discouraged.[18] The goal of parsimony in SEM is to preclude modifying a model solely to improve goodness-of-fit. In many instances, this merely takes advantage of chance correlations or sample-specific variances that have no logical or theoretical justification. The modifications noted here were added based on the empirical support and logic. For example, tumor size can affect pain and dyspnea, but without information on tumor size as a third variable causing the other two, the relationship between pain and dyspnea must be modeled as a correlation, indicating a spurious relationship that results from the third, unmeasured variable.

Fit information for the final models for both trials at both time points is presented in Table 1.

Results of the analyses suggested good fit of the hypothesized model (Fig 1) to the data in each trial and at both time points. The CFI was >0.95 for all four models (both trials, both time points), which is quite good. Another important fit index, the RMSEA, was an acceptable size, and the 90% CI was fairly tight for the two mBC models (baseline: 0.064, 90% CI = 0.000 to 0.116; cycle 3/week 6: 0.045, 90% CI = 0.000 to 0.110), indicating an acceptable RMSEA index and CI. In addition, these models failed to reject the close-fit hypothesis (ie, it was not significant) since the lower bound of the 90% CI included 0.05, also suggesting a reasonable fit of the model to the data. The RMSEA for the two NSCLC models was not as good as that for the mBC models, suggesting that the same model does not fit quite as well for this NSCLC sample as it does for the mBC sample. Nonetheless, the SRMR (which is the mean difference between model-estimated correlations and the actual observed correlations) was well below 0.1 in both trials and in all four individual models, indicating reasonable fit of the model to the data. That is, there was very minor discrepancy, on average, between the actual, observed correlations and the model-estimated correlations. Modification indices for all four models did not suggest any changes to the models that would improve fit, so no additional paths were added to any of the models.

In path analysis, the total effects of a relationship between two variables (ie, a correlation) are decomposed into a series of direct and indirect effects. Table 2 presents results of the model decomposition for the NSCLC trial at baseline, before the influence of any treatment, and Table 3 presents the decomposition results for the mBC trial population at baseline. It was deemed important to examine

TABLE 1. Goodness-of-Fit Information for AstraZeneca NSCLC (baseline and week 4) and Pfizer mBC Trials (baseline and week 6)

	Trial			
Fit Information	AZ NSCLC, Baseline	AZ NSCLC, Visit 5/Week 4	Pfizer mBC, Baseline	Pfizer mBC, Cycle 3/Week 6
Model X^2	37.702	38.455	13.506	9.481
Model df	7	7	7	7
Model *P* value	<.0001	<.0001	<.0001	<.0001
Null model X^2	1,563.103	1,251.887	924.223	892.941
Null model df	81	81	81	81
Null model *P* value	<0.0001	<0.0001	<0.0001	<0.0001
Δ X^2	1,525.401	1,213.432	910.717	883.460
Δ df	74	74	74	74
Δ *P* value	<0.001	<0.001	<0.001	<0.001
CFI	0.979	0.973	0.992	0.997
RMSEA	0.100	0.117	0.064	0.045
RMSEA 90% CI	0.070 to 0.133	0.083 to 0.154	0.000 to 0.116	0.000 to 0.110
Close-fit test *P* value	.004	.001	.276	.479
SRMR	0.039	0.044	0.029	0.028

Abbreviations: Δ X^2, difference in X^2 between the null model and the hypothesized model; CFI, comparative fit index; mBC, metastatic breast cancer; NSCLC, non–small cell lung cancer; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.

decomposition of effects at baseline only for purposes of comparing the hypothesized model across the two different cancers before treatment. Postbaseline yielded differences from baseline in some relationships between different symptoms and functional domains or GHS/QoL possibly because of the dissimilar effects of treatment, side effects of each treatment, or the way each disease responds to the respective treatment in each of the trials.

The results in both tables show that there are a much smaller number of direct effects of symptoms on the functional domains and GHS/QoL than there are indirect effects. In other words, the majority of effects of individual symptoms on the functional domains and GHS/QoL are indirect. For example, pain increases fatigue which reduces physical and role functioning which is associated with reduced GHS/QoL. Interestingly, dyspnea and fatigue are the most common symptoms to have direct effects on functional domains and GHS/QoL for patients in the NSCLC trial, whereas pain and fatigue are the symptoms that are more likely to have direct effects on these downstream domains for patients in the mBC trial. This is likely due, in part, to the different ways in which NSCLC and mBC affect patients and present symptoms. It is important to note that direct effects are generally smaller than total effects, because of the added influence of intervening variables (ie, indirect effects).

When comparing baseline and postbaseline decompositions, there are some notable differences in patterns of significant effects. There are twice as many differences between baseline and post-baseline decompositions for the mBC trial as there are for the NSCLC trial (Tables 4 and 5). For example, insomnia shows different patterns of significant effects with global health/QoL and with social functioning in the NSCLC trial: Insomnia has a larger effect on global health/QoL postbaseline but no effect on social functioning at post-baseline compared with baseline.

There are also differences in decomposition from baseline to postbaseline for the mBC trial: Dyspnea with global health/QoL and social functioning; insomnia with global health/QoL and social functioning; nausea/vomiting with physical functioning, social functioning, and emotional functioning; and appetite loss with physical functioning, social functioning, and emotional functioning. Dyspnea has a much smaller effect on global health/QoL and social functioning at postbaseline, and it is entirely indirect. Nausea/vomiting has a larger effect on physical functioning at postbaseline; a slightly larger, but indirect, effect on social functioning at postbaseline; and no effect on emotional functioning at postbaseline. Appetite loss has a larger effect on physical functioning, social functioning, and emotional functioning at postbaseline.

DISCUSSION

The objective of this study was to demonstrate that there is a causal cascade of effects from symptoms to patient functioning and HRQoL in single arms of two trials and that this set of relationships is similar when examining the QLQ-C30 in two types of cancers. The SEM/path analyses of these two trials, one for the treatment of NSCLC and the other for the treatment of mBC, showed very consistent patterns of relationships among the symptoms and functional domains of the QLQ-C30. Although these analyses used individual symptom items or composite scores for the multi-item domains (eg, fatigue and physical functioning), the general structure of the QLQ-C30 was retained for these analyses

TABLE 2. AZ NSCLC, Baseline: Total Effects, Direct Effects, and Total Indirect Effects of Symptoms on Functioning and Global Health/QoL

Dependent Variable	Explanatory Variable	Total Effects	Direct Effects	Total Indirect Effects
GLBLQOL	Nausea/vomiting	NS	NS	−.072**
GLBLQOL	Dyspnea	−.196***	−.108**	−.087***
GLBLQOL	Pain	−.354***	−.174***	−.180***
GLBLQOL	Insomnia	NS	NS	−.041*
GLBLQOL	Appetite loss	−.159**	NS	−.151***
GLBLQOL	Fatigue	−.394***	−.265***	−.128***
PHYSICAL	Nausea/vomiting	NS	NS	−.083**
PHYSICAL	Dyspnea	−.379***	−.272***	−.107***
PHYSICAL	Pain	−.275***	NS	−.215***
PHYSICAL	Insomnia	−.099*	NS	−.050*
PHYSICAL	Appetite loss	−.182***	NS	−.185***
PHYSICAL	Fatigue	−.482***	−.482***	NS
ROLE	Nausea/vomiting	−.127*	NS	−.113***
ROLE	Dyspnea	−.274***	−.196***	−.078***
ROLE	Pain	−.249***	NS	−.177***
ROLE	Insomnia	NS	NS	−.036*
ROLE	Appetite loss	−.285***	−.150***	−.135***
ROLE	Fatigue	−.353***	−.353***	NS
SOCIAL	Nausea/vomiting	NS	NS	−.067*
SOCIAL	Dyspnea	−.224***	−.083***	−.140***
SOCIAL	Pain	−.264***	NS	−.177***
SOCIAL	Insomnia	NS	NS	−.039*
SOCIAL	Appetite loss	−.149*	NS	−.144***
SOCIAL	Fatigue	−.375***	−.375***	NS
EMOTIONAL	Nausea/vomiting	−.114*	NS	−.078***
EMOTIONAL	Dyspnea	.140**	−.101*	−.039*
EMOTIONAL	Pain	−.226***	NS	−.210***
EMOTIONAL	Insomnia	−.279***	−.261***	NS
EMOTIONAL	Appetite loss	−.205***	−.138*	−.067**
EMOTIONAL	Fatigue	−.175**	−.175**	NS

Abbreviations: EMOTIONAL, emotional functioning; GLBLQOL, global health status/quality of life domain; NS, not significant; NSCLC, non–small cell lung cancer; PHYSICAL, physical functioning; ROLE, role functioning; SOCIAL, social functioning.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

to allow for consistency with previous work. The patterns of relationships and model fit were very similar across the two trials, which gave us confidence that the results are not unique to one type of cancer.

While the structure of the QLQ-C30 evaluated in this study was largely the same as that reported elsewhere,[12,19] explicitly modeling a causal cascade from symptoms through fatigue to functional domains and GHS/QoL received empirical support and these causal pathways seem to be logical. Furthermore, these results can help explain why the relationship between treatments and their effects on selected domains of the QLQ-C30 are often nonsignificant or inconsistent from study to study. The results of the present study strongly suggest that if analysts are exploring the effects of symptoms or symptom change on QLQ-C30 functional scales or GHS/QoL, most of these symptoms (except for pain and fatigue) would not show significant direct effects on the outcomes. Rather, anticipating a causal cascade from treatment or disease progression to symptoms, through pain and fatigue, to functional domains and GHS/QoL would yield more meaningful results.

The QLQ-C30 was developed more than three decades ago and has undergone revisions. Numerous modules have been developed to assess disease- and treatment-specific symptoms. An item library has been developed to allow for custom lists of questions that may be useful for rare diseases or side effects of more recent treatments, when the QLQ-C30 by itself may not be fit-for-purpose. The QLQ-C30 has been used in thousands of studies worldwide, and while the present study does not suggest that the QLQ-C30, as designed, is not an informative measure, it may be the way in which it is analyzed that needs revising. Based on the present

TABLE 3. American BioSciences, Inc, Metastatic Breast Cancer, Baseline: Total Effects, Direct Effects, and Total Indirect Effects of Symptoms on Functioning and Global Health/QoL

Dependent Variable	Explanatory Variable	Total Effects	Direct Effects	Total Indirect Effects
GLBLQOL	Nausea/vomiting	NS	NS	NS
GLBLQOL	Dyspnea	−.165**	NS	−.094**
GLBLQOL	Pain	−.393***	−.208**	−.185***
GLBLQOL	Insomnia	NS	NS	NS
GLBLQOL	Appetite loss	NS	NS	−.057*
GLBLQOL	Fatigue	−.336***	−.336***	NS
PHYSICAL	Nausea/vomiting	NS	NS	−.075*
PHYSICAL	Dyspnea	−.258***	−.159**	−.100**
PHYSICAL	Pain	−.502***	−.314 NS	−.188***
PHYSICAL	Insomnia	NS	NS	NS
PHYSICAL	Appetite loss	NS	NS	−.060*
PHYSICAL	Fatigue	−.355***	−.355***	NS
ROLE	Nausea/vomiting	−.115*	NS	−.097*
ROLE	Dyspnea	−.132*	NS	−.108***
ROLE	Pain	−.556***	−.334***	−.221***
ROLE	Insomnia	NS	NS	NS
ROLE	Appetite loss	−.161*	NS	−.065*
ROLE	Fatigue	−.383***	−.383***	NS
SOCIAL	Nausea/vomiting	NS	NS	NS
SOCIAL	Dyspnea	−.214**	NS	−.076*
SOCIAL	Pain	−.455***	−.234**	−.221***
SOCIAL	Insomnia	−.137*	−.128*	NS
SOCIAL	Appetite loss	NS	NS	−.046*
SOCIAL	Fatigue	−.271**	−.271**	NS
EMOTIONAL	Nausea/vomiting	−.178*	NS	NS
EMOTIONAL	Dyspnea	NS	NS	NS
EMOTIONAL	Pain	−.300***	NS	.215**
EMOTIONAL	Insomnia	−.258***	−.255***	NS
EMOTIONAL	Appetite loss	NS	NS	NS
EMOTIONAL	Fatigue	NS	NS	NS

Abbreviations: EMOTIONAL, emotional functioning; GLBLQOL, global health status/quality of life domain; NS, not significant; PHYSICAL, physical functioning domain; ROLE, role functioning; SOCIAL, social functioning.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

analyses, the QLQ-C30 can be informative about a patient's response to their disease or treatment. Furthermore, the relationships among the various symptoms and domains are more complex than typical analyses can demonstrate. Consequently, if future analyses do not explicitly model the indirect effects of treatment through symptoms, particularly modeling the central role that fatigue plays in this causal cascade, those analyses are likely to underestimate the effects of treatment on functional and GHS/QoL domains.

Modeling this cascade among the QLQ-C30 items/domains and thus gaining an understanding of these complex causal relationships does not require using a structural equation modeling approach. Selected pathways can be examined using multiple regression in a path analytic context. The advantage of the SEM approach is that all variables, including manifest and latent (unmeasured) variables (ie, factors) for measurement and structural portions of a model, can be examined in a single analysis, obtaining an overall fit of the model to the data.

For both patient populations, pain and fatigue appear to be particularly salient mediators between specific symptoms of NSCLC or mBC and functional and GHS/QoL domains. Moreover, treatments are most likely to have direct effects on specific symptoms, which will have downstream effects on the functional and GHS/QoL domains, rather than treatments having direct effects on these domains.

These analyses did not test for causal relationships among the functional and GHS/QoL domains of the QLQ-C30. The basic assumption is that for these two trials, at least, these

TABLE 4. AZ NSCLC, Visit 5/Week 4: Total Effects, Direct Effects, and Total Indirect Effects of Symptoms on Functioning and Global Health/QoL

Dependent Variable	Explanatory Variable	Total Effects	Direct Effects	Total Indirect Effects
GLBLQOL	Nausea/vomiting	NS	NS	−.073**
GLBLQOL	Dyspnea	−.288***	−.181**	−.107***
GLBLQOL	Pain	−.270***	NS	−.220***
GLBLQOL	Insomnia	−.123*	NS	NS
GLBLQOL	Appetite loss	−.243***	−.152**	−.091***
GLBLQOL	Fatigue	−.307***	−.307***	NS
PHYSICAL	Nausea/vomiting	NS	NS	−.094**
PHYSICAL	Dyspnea	−.389***	−.212***	−.177***
PHYSICAL	Pain	−.324***	NS	−.297***
PHYSICAL	Insomnia	−.108*	NS	NS
PHYSICAL	Appetite loss	−.314***	−.163**	−.151***
PHYSICAL	Fatigue	−.507***	−.507***	NS
ROLE	Nausea/vomiting	NS	NS	−.063*
ROLE	Dyspnea	−.369***	−.185***	−.184***
ROLE	Pain	−.324***	NS	−.231***
ROLE	Insomnia	NS	NS	NS
ROLE	Appetite loss	−.211***	NS	−.157***
ROLE	Fatigue	−.528***	−.528***	NS
SOCIAL	Nausea/vomiting	NS	NS	NS
SOCIAL	Dyspnea	−.234***	−.175**	−.059*
SOCIAL	Pain	−.157*	NS	−.100*
SOCIAL	Insomnia	NS	NS	NS
SOCIAL	Appetite loss	−.119*	NS	−.050*
SOCIAL	Fatigue	−.168*	−.168*	NS
EMOTIONAL	Nausea/vomiting	−.114*	NS	−.052**
EMOTIONAL	Dyspnea	.213***	−.159**	NS
EMOTIONAL	Pain	−.174**	NS	−.214***
EMOTIONAL	Insomnia	−.265***	−.250***	NS
EMOTIONAL	Appetite loss	−.173**	NS	NS
EMOTIONAL	Fatigue	NS	NS	NS

Abbreviations: EMOTIONAL, emotional functioning; GLBLQOL, global health status/quality of life domain; NS, not significant; NSCLC, non–small cell lung cancer; PHYSICAL, physical functioning; ROLE, role functioning; SOCIAL, social functioning.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

are all relatively important domains for patients and the salience of each domain is reflected in the path coefficients from pain and fatigue to each of the functional/QoL domains. Thus, it would be difficult with these data to demonstrate, logically and empirically, that one or more functional domains is antecedent to other functional domains with, perhaps, GHS/QoL being the ultimate outcome variable. This could, however, be assessed using more than one time point for the analysis. For NSCLC and mBC, the choice of one or more functional or GHS/QoL domains as a trial or clinical practice end point may come down to what is most relevant to the patients, and this may vary as a function of the specific treatment they are receiving.

The present analyses used data from one arm of each of two different trials (most of the data available from Project Data Sphere include only the comparator arms of clinical trials submitted to their data repository). Thus, there was no opportunity to test the effects of treatment in these causal cascades. The importance of modeling indirect effects of treatment on selected outcomes has been demonstrated elsewhere. For example, in a study of the effects of erythropoiesis-stimulating agents (ESAs) and patient-report fatigue in chemotherapy-induced anemia, results of latent growth modeling (a type of SEM) demonstrated that the ESA, darbepoetin alfa, had an *indirect* effect on patient-reported fatigue through its influence on hemoglobin.[8] This was seen in data from four clinical trials. The *direct* effect of darbepoetin alfa on patient-reported fatigue was, however, nonsignificant, demonstrating that analyses need to model the more complex causal cascade among variables of interest.

When using SEM to evaluate a causal cascade, the analyst has options of including treatment as an exogenous variable in

TABLE 5. American BioSciences, Inc, Metastatic Breast Cancer, Cycle 3/Week 6: Total Effects, Direct Effects, and Total Indirect Effects of Symptoms on Functioning and Global Health/QoL

Dependent Variable	Explanatory Variable	Total Effects	Direct Effects	Total Indirect Effects
GLBLQOL	Nausea/vomiting	NS	NS	NS
GLBLQOL	Dyspnea	NS	NS	−.110***
GLBLQOL	Pain	−.427***	−.234***	−.193***
GLBLQOL	Insomnia	−.205**	−.170*	NS
GLBLQOL	Appetite loss	NS	NS	−.102**
GLBLQOL	Fatigue	−.356***	−.356***	NS
PHYSICAL	Nausea/vomiting	−.161*	NS	−.085*
PHYSICAL	Dyspnea	−.250***	NS	−.142**
PHYSICAL	Pain	−.494***	−.327***	−.167***
PHYSICAL	Insomnia	NS	NS	NS
PHYSICAL	Appetite loss	−.202*	NS	−.131***
PHYSICAL	Fatigue	−.459***	−.459***	NS
ROLE	Nausea/vomiting	−.131*	NS	−.095*
ROLE	Dyspnea	−.215**	NS	−.162***
ROLE	Pain	−.419***	−.182*	−.237***
ROLE	Insomnia	NS	NS	NS
ROLE	Appetite loss	−.220*	NS	−.150***
ROLE	Fatigue	−.525***	−.525***	NS
SOCIAL	Nausea/vomiting	NS	NS	−.095*
SOCIAL	Dyspnea	NS	NS	−.170***
SOCIAL	Pain	−.416***	−.186*	−.229***
SOCIAL	Insomnia	NS	NS	NS
SOCIAL	Appetite loss	−.213**	NS	−.158***
SOCIAL	Fatigue	−.551***	−.551***	NS
EMOTIONAL	Nausea/vomiting	NS	NS	NS
EMOTIONAL	Dyspnea	NS	NS	NS
EMOTIONAL	Pain	−.348***	−.203*	−.145**
EMOTIONAL	Insomnia	−.194**	−.187**	NS
EMOTIONAL	Appetite loss	−.150*	NS	NS
EMOTIONAL	Fatigue	NS	NS	NS

Abbreviations: EMOTIONAL, emotional functioning; GLBLQOL, global health status/quality of life domain; NS, not significant; PHYSICAL, physical functioning domain; ROLE, role functioning; SOCIAL, social functioning.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

which the influence of treatment is examined on each of the variables in the rest of the model (seen in Fig 1), but where treatment would be on the far left of the model. Alternatively, the SEM analysis can be conducted as a multigroup analysis where treatment is included as a known-group variable. In this case, the model is analyzed for each group and the analyst can test empirically to see whether there are significant differences between treatment arms. This would demonstrate whether the model fits equally well for both treatment arms and whether one treatment has stronger direct, indirect, and total effects on symptoms, functioning, and HRQoL.

While the analyses in this study focused on contemporaneous effects of QLQ-C30 symptoms, functional domains, and HRQoL, the analyst could also explore lagged effects of these relationships. For example, does pain affect fatigue at a later cycle of treatment in addition to current fatigue? This is a simple extension of the models examined in this study.

The present analyses validate results presented by others[3-5,8,9] and provide evidence that it is important to thoroughly conceptualize and anticipate relationships among variables of interest. Our results recognize that many of these relationships are likely to be indirect, with potentially many degrees of separation between the variables under study. Thus, in studies of cancer treatments, the treatment is likely to have an indirect effect on patient-reported outcomes through other symptoms, such as pain and fatigue.

We hope that these results will help researchers understand why there may not be significant effects of treatment on

functional or QoL domains: the relationships are more complex and require modeling these more complex causal pathways. Furthermore, these results may corroborate clinical experience, where physicians see changes in patients' functional domains or QoL after treatment, although the results of standard clinical trial analyses may not bear out these findings. Whether researchers use SEM or regression-based analyses, it seems clear from our results that the effects of symptoms for patients with NSCLC and mBC will be better understood when these more complex causal pathways are anticipated and analyzed. It is unlikely that SEM will replace the current battery of analytic methods for clinical trial data in the near future since those methods are well-entrenched. However, SEM can be used for most of the same analyses, such as survival analysis, mixed model repeated measures (MMRM), and growth modeling. In the current study, no measurement component was included and SEM was used to address a specific structural question involving only manifest (observed) variables: Can we show, empirically, how several symptoms, functional domains, and HRQoL are related via a complex set of pathways in a single analysis? SEM can provide additional insights into the patient's experience with their disease and treatment beyond overall survival or PFS.

AFFILIATION

[1]Patient Centered Solutions, IQVIA, New York, NY

CORRESPONDING AUTHOR

Donald E. Stull, PhD; e-mail: Donald.stull@iqvia.com.

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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