Patient-reported outcomes and importance of their appropriate statistical analyses

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With medical care reimbursement now tied to patients’ experience and health status, patient-reported measures (PRMs) are becoming an important gauge of patient-perceived value of medical care. PRMs can be generic or disease specific. The 36-Item Medical Outcomes Study Short-Form, measuring general physical and mental domains of quality of life, and the Hospital Consumer Assessment of Healthcare Providers and Systems survey, measuring patient satisfaction with their medical care experience, are examples of generic PRMs. A “classic” health status generic PRM is the Wong–Baker pain intensity score,1 usually recorded in the hospital. The Kansas City Cardiomyopathy Questionnaire,2 designed to monitor the perceived functional health status (or health-related quality of life) of patients with heart failure, and the Neuro-Quality of Life,3 which measures functional health status of patients with neurologic disorders, are examples of disease-specific PRMs.

Fagundes and colleagues4 used the MD Anderson Symptom Inventory to assess patient-reported outcomes. This disease-specific PRM of severity of cancer-related symptoms strengthens their findings. Because of ease of implementation, most investigators focus only on PRMs collected in the hospital. Fagundes and colleagues4 studied patient-reported outcomes collected during the first 3 months after surgery. More data add strength to their inferences.

Data collected repeatedly over time for each patient in a study are called longitudinal data. The important feature of longitudinal data is that although the observations between patients are assumed to be uncorrelated, the observations from a single patient are correlated to some degree. Thus, statistical analyses or models that involve longitudinal data should consider such correlation to draw valid inferences. It is also important to understand statistical models that consider these features. We believe that any longitudinal data analysis using medical data should include (1) temporal trend of the longitudinal response over time and (2) factors influencing that trend. Understanding these factors and possible interactions with time could greatly assist physicians and surgeons in interpreting outcomes data and using them to better manage patients.

In observational studies, we often encounter so-called unbalanced data, with different numbers of observations collected at different times for each patient. Laird and Ware5 introduced the random-effects model in a longitudinal setup for continuous data, wherein the correlation among observations for a given subject is accounted for by using unobservable random effects. Random-effects models can easily handle unbalanced longitudinal data. Use of nonlinear mixed-effect models to analyze medical longitudinal data has been increasing. By using flexible parametric,6 semiparametric, or nonparametric mixed-effects models, one can investigate individual (patient-specific) profiles as well as overall profile.

Most PRMs are recorded as a series of ordered categories, such as intensity of pain on a 0 to 10 scale. Such data warrant use of statistical models that exploit the ordinal nature of the data. The cumulative or graded response model (McCullagh7) is a popular method for analyzing ordinal response data. Collecting these data over time provides longitudinal ordinal data, frequently analyzed using the cumulative logistic mixed-effects model. However, because of ease of application and interpretation, most outcome studies analyze these ordinal data as continuous. When there are many individual categories of ordinal data, it is acceptable to do this. However, in
general, analyzing outcomes as a different data type is a major flaw.

Another common way that longitudinal data are mishandled is changing the longitudinal response into a time-to-event response by applying a threshold in the longitudinal outcome. Although this may provide simplicity in application and interpretation, time of transition from one response level to another is generally nonobservable and discards too much important information, leading to less valid inferences. When the longitudinal trend is nonlinear, as in longitudinal responses in most observational medical research studies, changing longitudinal data into time-to-event data generally yields invalid inferences. Therefore, analyzing an outcome as its own data type using the correct statistical model is an important aspect of data analysis. Fagundes and colleagues add strength to their article by analyzing longitudinal ordinal data using the cumulative logistic mixed-effects model. One important drawback of their study, despite their valid clinical reasoning, is that time to recovery was assessed by changing longitudinal data into time-to-event data.

Another major aspect of longitudinal data analysis, where time of measurement plays an important role, is that a risk factor’s influence can change over time. That is, there may be an interaction effect between time and the risk factor. We believe this should be an important component of longitudinal data analysis, particularly when investigating outcomes after an intervention, because different sets of risk factors can affect an outcome at different times. Fagundes and colleagues have extensively investigated this feature.

Fagundes and colleagues investigated several longitudinal variables. When there is more than 1 longitudinal outcome and the focus of the analysis is to assess the effect of a certain variable (or variables) on all longitudinal outcomes, the preferable approach is multivariate longitudinal analysis. However, this methodology is evolving and is an area of active statistical research.

References