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METHODOLOGICAL ARTICLES

Identifying Differential Responders and Their Characteristics in Clinical Trials: Innovative Methods for Analyzing Longitudinal Data

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ABSTRACT

Objectives: To present a step-by-step example of the examination of heterogeneity within clinical trial data by using a growth mixture modeling (GMM) approach. **Methods:** Secondary data from a longitudinal double-blind clinical drug study were used. Patients received enalapril or placebo and were followed for 2 years during the drug component, followed by a 3-year postdrug component. Primary variables of interest were creatinine levels during the drug component and number of hospitalizations in the postdrug component. Latent growth modeling (LGM) methods were used to examine the treatment response variability in the data. GMM methods were applied where substantial variability was found to identify latent (unobserved) subsets of differential responders, using treatment groups as known classes. Post hoc analyses were applied to characterize emergent subgroups. **Results:** LGM methods demonstrated a large variability in creatinine levels. GMM methods identified two subsets of patients for each treatment group. Placebo class 2 (7.0% of the total sample) and enalapril class 2 (8.5%) include individuals whose creatinine levels start at 1.114 mg/dl and 1.108 mg/dl, respectively, and show worsening (slopes: 0.023 and 0.017, respectively). Placebo class 1 (43.1%) and enalapril class 1 (41.4%) individuals start with lower creatinine levels (1.082 and 1.083 mg/dl, respectively) and show very minimal change (0.008 and 0.003, respectively). Post hoc analyses revealed significant differences between placebo/enalapril class 1 and placebo/enalapril class 2 in terms of New York Heart Association functional ability, depression, functional impairment, creatinine levels, mortality, and hospitalizations. **Conclusions:** GMM methods can identify subsets of differential responders in clinical trial data. This can result in a more accurate understanding of treatment effects.

Keywords: differential responders, heart failure, heterogeneity, mixture model.

Introduction

Variability in response to treatment is a common finding in clinical trials, and the study of this has received particular attention in recent years [1–4]. Patients assigned to treatment arms come from different backgrounds with different genetic makeups, life situations, experiences, and stressors. In designing clinical trials, randomization is used to ensure comparable groups prior to treatment, reducing the chances that differences in treatment response are the result of preexisting differences between treatment groups. Despite these efforts, differential treatment response can still exist; that is, not all patients in treatment groups respond in the same way or to the same extent. This can disguise true treatment effects and potentially mask the value of products for particular patients by increasing the mean response where there is a class of hyperresponders or, conversely, decreasing the mean response where there is a class of hypo- or nonresponders [5]. That is, some patients in active treatment groups may show no response, or deterioration, and when their results are analyzed together with the results of responsive patients, the overall treatment effect is dampened. In addition, some patients in placebo groups may show a "treatment response" when such response is not expected or warranted. Understanding which particular patients are more, or less, likely to benefit from treatment is important to ensure that medicine is administered optimally. That is, identifying patients for whom treatment is effective can aid the development of personalized medicine.

An indicator that differential response, or heterogeneity, is present within clinical trial data is the presence of variability in scores for end points during, or at the end of, a study [6]. Identifying these differential responders obviously has advantages for understanding treatment effect. Such detailed information may provide clues that can be used to move us closer to personalized medicine. These insights can aid in designing clinical trials that are more appropriately powered, include the most relevant patients, help minimize the exposure to potentially toxic treatments of those patients who are likely to be the least

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responsive, and reduce the cost and burden of administering treatment to such patients.

Of course, some variability in clinical trials is hypothesized and expected, such as differences between treatment and placebo groups, across doses, or between comparator drugs. Thus, multigroup analyses are typically performed to compare the magnitude of responses between explicitly defined subgroups (e.g., treatment and placebo). Latent growth modeling (LGM) method, a structural equation modeling (SEM) approach, represents a type of analytic method used to compare predefined subgroup responses to an intervention [7–9]. LGM methods have an advantage over methods such as analysis of variance (ANOVA) or multiple regression in that they can use information from all assessment points in a single model, control for time-invariant and time-varying covariates, explicitly model measurement error, and can include multiple outcome variables simultaneously, including (but not limited to) clinical, clinician-reported, and patient-reported outcomes.

We can define as follows a straight linear LGM method involving two latent constructs (intercept and slope) in which a continuous variable, y, is measured across four time points [10]:

$$y_i = \Lambda_y \eta + \varepsilon_i \quad (1)$$

where y_i is a $p \times 1$ vector of repeated measures containing scores for individual i (1, 2,…, n) at t ($t = 1, 2,\ldots, 4$) occasions, η is defined as an $m \times 1$ vector that contains the intercept and linear growth factors, and Λ_y is a $p \times m$ design matrix (in the present study, a 4×2 matrix, for four occasions and one intercept and one slope factor). ε_i is a $p \times 1$ vector (in the present case, a 4×1) of time-specific residuals for each individual i.

A key assumption of LGM methods is that the growth trajectories (slopes of change) for all individuals can be represented with a single, common slope parameter [11]. That is, all individuals show similar changes over time on a given measurement. However, as discussed above, this assumption may be untenable in some circumstances for any number of reasons (e.g., different genotypes, differences in health care use outside the trial protocol, differences in concomitant medication use, and differences in family or social support). Differences between individuals can result in qualitatively and quantitatively different slopes of change over time [4,5].

When analytic methods using predefined groups account for only part of the variability in response to treatment (i.e., individuals within treatment groups continue to exhibit different change patterns), the analyst may suspect that there are subgroups of differential responders within the trial and must consider other techniques. Some of the heterogeneity in treatment response may be attributable to unobserved but potentially identifiable factors, such as genetics. Some may be the result of observed variables that are included as covariates in analyses (e.g., age, gender, dose, and comorbidities). Still other components of the variability may involve data that are collected as part of the trial but are not explicitly included as covariates in analyses, including baseline levels and changes in variables. Finally, treatment response variability could involve contextual variables outside the study (e.g., different standards of care across countries in a multicountry trial). In the latter two examples, the cause of heterogeneity in response must be inferred from the data.

While various approaches can be used to uncover subgroups of differentially responsive patients, they may introduce problems with multiple comparisons or require substantial amounts of time to conduct the many different subgroup analyses. For example, in the absence of a predefined criterion for a nonresponder, responder, or partial responder, using a traditional approach an analyst must make multiple comparisons trying different cutoff values in a variable of interest, violating assumptions of independence. In such circumstances, the search for differential responders may require dozens or hundreds of data slices to find those particular patients, model their slope parameters, and determine their characteristics. Obviously, this is not an efficient, nor a scientifically rigorous approach.

Numerous methods, historically, have been available to evaluate heterogeneity in data, including discriminant analysis, multigroup common factor analysis, latent class analysis, and latent profile analysis. Only the latter three evaluate the data in terms of a latent (i.e., unobserved) construct accounting for class assignment [12]. More recently, methods based on SEM have been developed and used to evaluate the existence of latent classes within heterogeneous data. Mixture models—factor mixture models and growth mixture models—are a combination of common factor and latent class analysis and can allow analysts to explore patterns of means, variances, and covariances in the existing data to uncover groups of differential responders [11–13].

Latent variable mixture modeling relaxes the assumption of LGM that all respondents are drawn from the same population and thus have a common underlying slope of change. Growth mixture modeling (GMM) captures the heterogeneity in slopes of change within the population by modeling distinct subpopulations through incorporating a latent categorical variable [10,12].

Suppose we begin with a growth model and hypothesize that three distinct growth curves ($k = 3$ classes) account for the heterogeneity of patient response to treatment, then Equation 1 is extended very simply:

$$y_{ik} = v_k + \Lambda_k \eta_{ik} + \varepsilon_{ik} \quad (2)$$

where $k = 1, 2, 3$ classes and $i = 1, 2,\ldots n$ cases. An additional term, v_k, is added to represent the intercepts of the continuous observed variables y for each class, k. In a latent growth curve model, the y-intercept vector, v, is set to zero and the latent means are estimated. By including the latent trajectory classes ($k = 1, 2, 3$), it allows for heterogeneity of slopes of change (i.e., treatment response) within the larger population of patients.

These methods can be used with cross-sectional (factor mixture models) or longitudinal data (growth mixture models) to explore unobserved subclass homogeneity within observed population heterogeneity. That is, these analytic methods can uncover a subset(s) of patients who exhibit within-class homogeneity yet are themselves different from the larger class of patients from which they are drawn. Such subsets can be examined post hoc to see what variables may account for their class membership, thus differentiating them from the remaining patients. Several articles that cover this topic have been published, such as Muthén and Asparouhov [14], who outline examples of the GMM framework and how this has been applied to longitudinal studies. Muthén et al. [4] outlined the application of GMM approaches to a small-scale clinical trial of depression medication and demonstrated successful identification of subsets of differential responders within different treatment arms. Identification of groups of differential responders within treatment arms is a big step toward furthering the development and refinement of personalized medicine and should ideally become a standard approach when analyzing clinical trial data. The present article builds on previous work by presenting a step-by-step guide to examining and modeling heterogeneity within longitudinal large-scale clinical trial data. Moreover, the article demonstrates how to identify the specific variables belonging to different subsets of differential responders that may account for their class membership, through post hoc comparisons between latent classes. While the goal is to provide a step-by-step example of conducting these analyses using longitudinal data, along with some of the potential problems and unresolved issues to be