Commentary: Linear mixed-effect models in longitudinal data analysis: Shaken not stirred

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Central Message

Linear mixed models are powerful statistical methods in clinical research but require careful preparation and accurate planning.

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In this issue of the *Journal*, Heo and colleagues[1] present an interesting study on the impact of the intimal tear on the aortic destiny after total arch replacement (TAR) in repairing type I aortic dissection. The hypothesis of this study was that the location of the intimal tear after surgery would represent the most important factor affecting both the dilatation of the aorta and the incidence of reintervention. To explore this hypothesis, the authors had a dataset of 85 patients who underwent TAR, and 40 of them have been investigated over time with serial computed tomography scans. Therefore, they had to analyze the same variables measured over multiple and different time points: This type of database is defined as a longitudinal dataset and requires a carefully planned statistical analysis. In fact, when evaluating a variable that changes over time, it has to be considered that the observations are not independent of each other and that the individual variance has an impact on the outcome, possibly representing a bias on the overall analysis.

Statistical techniques that assume independent observations, such as linear regression, cannot be used in this context, and the need for addressing intra-individual correlation has triggered the development of alternative models.[2] Linear mixed-effect models are very useful when analyzing longitudinal data, especially when there are missing values, there are more than 2 time points, or there is a need for adjusting for other confounding factors. In this approach, one can account for unobservable differences between individuals by specifying specific effects that can vary over subjects.[3]

"Mixed-effect modeling" means that there are 2 type of effects: a fixed effect, which is the one of interest for interpretation of the results, and a random effect, which in most cases is not of interest for interpretation of the results. Therefore, some parameters can vary between subjects ("random"), whereas others cannot change between subjects ("fixed"). For instance, in a longitudinal study, the individual subjects could be considered as a random effect or in a multicenter nonlongitudinal surgical study, the individual center (or even the individual surgeon) might be considered as a random effect. After specifying the random effect in the model, the differences between predicted and observed values of the outcome are considered conditionally independent. In a linear mixed-model effect, both the intercept and the slope can be considered as random: In a random intercept model, we account for baseline differences and assume that the effect of the variables of interest is going to be the same for each individual. In the random slope model, used in Heo and colleagues' study,[1] the subjects are allowed to have different intercepts, but also different slopes for the effect of the variable of interest. With this type of approach, the authors have been able to clearly define the factor affecting the fate of the aorta after TAR and have identified the importance of the residual tear location in the proximal descending thoracic artery. Their study is also a good example of integration of medical and statistical knowledge, for instance, they have decided to exclude the first follow-up computed tomography scans in the linear mixed model because these scans were performed after a short period of time after the surgery, probably too short to evaluate the stabilization of the intimal flap. This clinical rationale probably would have been missed by a pure statistician.

As we can see, multiple different considerations have to be taken into account when planning a linear mixed model for longitudinal data. The correct mixture of random and fixed effect and the use of covariates have to be carefully dosed before introducing them into the final "recipe." As James Bond would say: Shaken, not stirred.

References

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