Generalized Estimating Equations vs. repeated-measures ANOVA on the time-course of clinical variables during acute exacerbations of chronic obstructive pulmonary disease

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Introduction

Health outcomes research is aimed to “understand the end results of particular health care practices and interventions” [1], to inform the development of clinical guidelines, evaluate the quality of healthcare, and foster effective health interventions. It is, therefore, essential to have longitudinal information that encompasses the natural course of common diseases and the long-term outcomes of healthcare and treatments to promote evidence-based decision making. However, longitudinal studies are often punctuated by the presence of missing data which may compromise the representativeness of the sample and lead to biased results. Repeated-measures analysis of variance (rmANOVA) is widely used to analyse outcomes of longitudinal health-related studies, however it does not handle missing data and may influence the outcomes achieved. Generalized estimating equations (GEE) is a statistical method that belong to a class of semiparametric regression techniques and is less sensitive to variance structure specification. Although widely used in methodological areas, the GEE has been scarcely applied in clinical contexts. This study compares the results achieved using the rmANOVA and the GEE to analyse the time-course of clinical variables during acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and explore the factors influencing this recovery period.

Methods

A longitudinal observational study was conducted in non-hospitalised patients with AECOPD recruited from the urgent care of a Central Hospital. Approval was obtained from the ethics committee of the Centro Hospitalar do Baixo Vouga (13NOV’1514:40065682) and from the National Data Protection Committee (8828/2016). Written informed consent was obtained before data collection.

Patients were asked to attend to four assessment sessions: within 48 hours of the urgent care visit (T0), and approximately 8 days (T1), 15 days (T2), and 45 days after the hospital visit (T3). At T0, the body mass index (BMI), the Charlson comorbidity index (CCI), the

number of exacerbations in the previous year and the modified British Medical Research Council (mMRC) questionnaire for dyspnoea were collected (independent measures). Additionally, in each data collection moment, peripheral oxygen saturation (SpO_2), forced expiratory volume in one second, in percentage of the predicted value (FEV_1pp), the chronic obstructive pulmonary disease (COPD) assessment test (CAT) and the five-repetition sit-to-stand test (5STS) were collected.

Assumptions of the rmANOVA (i.e., multivariate normal distribution and sphericity) were evaluated with the Q-Q plots, for each variable, and the Mauchly's test of sphericity. Assumptions of the GEE (i.e., missingness at random) [2] were tested with the Little's missing completely at random (MCAR) test. Both methods were then applied to the data, acknowledging that the rmANOVA excludes subjects with at least one missing value. The GEE was used with a gamma link function and independent correlation structure.

Results

Forty-four non-hospitalised patients with AECOPD (31 males; 68±9 years; 51±20 FEV_1pp) agreed to participate in the study. Using the rmANOVA, only patients that completed all measures were analysed, meaning that data from 36 participants were used for the CAT, 35 for SPO_2, 29 for the 5STS and 25 for the FEV_1pp. Data from 44 patients were used when applying the GEE, except for the BMI covariate since data of 5 participants were missing. Assumptions for both statistical approaches were verified.

Considering $p<0.05$ and $p<0.01$, consistency (i.e., both analysis provided simultaneously either significancy or not significancy) between the rmANOVA and the GEE was found in 78% of the results (28/36 comparisons) and differences in 22% (8/36) of the results. From those, 5% (2/8) were detected as significant only by the rmANOVA and 17% (6/8) only by the GEE (tables 1 and 2). Considering $p<0.01$, consistency was found in 81% (29/36) of the results and differences in 19% (7/36) of the results. From those, 5% (2/7) were detected as significant only by the rmANOVA and 14% (5/7) only by the GEE

Table 1. Within- subjects and between- subjects results.

	Repeated-measures ANOVA				GEE			
	SpO_2	FEV_1pp	CAT	5STS	SpO_2	FEV_1pp	CAT	5STS
Time		✓	✓	✓	✓	✓	✓	✓
BMI			✓			✓	✓	
CCI				✓				✓
Exacerbations	✓				✓			
mMRC	✓		✓				✓	

Legend: 5STS, 5 times sit-to-stand; BMI, body mass index; ANOVA, analysis of variance; CAT, COPD assessment test; CCI, Charlson comorbidity index; FEV_1pp, forced expiratory volume in one second, percentage predicted; GEE, Generalized estimating equations; mMRC, Modified British Medical Research Council questionnaire; SpO_2, peripheral oxygen saturation. ✓$p<0.05$

Table 2. Interaction results (i.e., time vs. co-variates).

	Repeated-measures ANOVA				GEE			
	SpO_2	FEV_1pp	CAT	5STS	SpO_2	FEV_1pp	CAT	5STS
Time								
BMI							✓	✓
CCI								✓
5STS								
Exacerbations								
mMRC		✓						✓

Legend: 5STS, 5 times sit-to-stand; BMI, body mass index; ANOVA, analysis of variance; CAT, COPD assessment test; CCI, Charlson comorbidity index; FEV_1pp, forced expiratory volume in one second, percentage predicted; GEE, Generalized estimating equations; mMRC, Modified British Medical Research Council questionnaire; SpO_2, peripheral oxygen saturation. ✓$p<0.05$

Discussion

Significant results were found using rmANOVA and GEE, however differences in the results obtained with both methods emerged. Previous studies have shown that GEE is more efficient than rmANOVA as it presents higher statistical power with smaller sample sizes and numbers of repeated measures [3], thus using a small sample size for the rmANOVA may have contributed for the different results achieved. Additionally, even with a high percentage of missing data (~70%), GEE estimates the effect under the outcome variable with smaller standard errors than analyses performed using the complete data only [4]. Nevertheless, the choice of the most adequate statistical approach to use should be based on the nature of

data (i.e., missingness of random and normality of data) and aims of the analysis to be conducted.

Conclusion

The choice of the statistics method impacts on our understanding of the behaviour of clinical variables during AECOPD which ultimately may affect clinical decision-making and production of guidelines.

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References

[1] Chumney EC. Methods and designs for outcomes research: ASHP; 2006.

[2] Ghisletta P, Spini D. An Introduction to Generalized Estimating Equations and an Application to Assess Selectivity Effects in a Longitudinal Study on Very Old Individuals. J Educ Behav Stat. 2004;29:421-37. URL: https://journals.sagepub.com/doi/10.3102/10769986029004421

[3] Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: advanced statistical methods for the analysis of longitudinal data in anesthesia research. Reg Anesth Pain Med. 2012;37:99-105. URL: https://rapm.bmj.com/content/37/1/99.long

[4] Fairclough DL, Thijs H, Huang IC, Finnern HW, Wu AW. Handling missing quality of life data in HIV clinical trials: what is practical? Qual Life Res. 2008;17:61-73. https://link.springer.com/article/10.1007/s11136-007-9284-3