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Analyzing health-related quality of life using longitudinal random-effects growth curve models in cardiology: a simulation study

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Abbreviations: HRQoL, health-related quality of life; QoL, quality of life; KCCQ, Kansas city cardiomyopathy questionnaire; SF-36, 36-item short-form health survey; EQ-5D, euro-qoL-5D; GCM, growth curve model; ANC, analysis of covariance

Introduction

Health-related quality of life (HRQoL) is a key endpoint in cardiovascular clinical trials for evaluating treatment efficacy and interpreting clinical outcomes in the context of an individual's health status as well as providing information about the benefits of alternative health interventions. HRQoL instruments like the EQ-5D and SF-36 are designed to evaluate generic quality of life applicable across all diseases, medical interventions and across a wide range of populations.[1] In contrast, one of the widely used HRQoL instrument in cardiovascular clinical trials that is used to assess disease specific health status is the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered questionnaire that has been shown to be a reliable and valid measure of symptoms, functional status, and quality of life in patients with heart failure symptoms, including aortic stenosis and mitral regurgitation. The KCCQ assesses specific health domains like physical limitation, symptoms, quality of life, social limitation, and self-efficacy–the first 4 of which are combined into an overall summary score labeled KCCQ-OS. Values for all KCCQ domains and the summary score range from 0 to 100, with higher scores indicating less symptom burden and better quality of life. Changes in KCCQ-OS scores of 5, 10, and 20 points correspond to small, moderate, or large clinical improvements, respectively.[2]

In cardiovascular clinical trials aiming to evaluate disease specific HRQoL in heart failure patients, the primary QoL endpoint is the KCCQ-OS score. All other KCCQ domain scores and generic QoL measures like the SF-36 physical, mental component score, and EQ-5D utility scores are considered secondary. For each of the primary and secondary health status outcomes, longitudinal random-effects growth curve models are used to examine the relative effect of the novel treatment versus control group over time. These growth curve models incorporate all available health status data from all follow-up time points, including those for patients who subsequently died, withdrew from the study, or were lost to follow-up[2]. Growth curve models that borrow too much information from the earlier QoL assessments resulting in some early QoL benefit being carried in to the later timepoints in a trial with many follow-up data points, effect that is absent in the raw data and other statistical models like analysis of covariance present a scenario highlighting the need for standardization of statistical methods used in the analysis of HRQoL data. The objective of this study is to demonstrate the application of random-effects growth curve models and compare the results with analysis of covariance through a simulation study.

Simulation algorithm

Simulation can be used to reveal the extent to which different statistical approaches lead to different inferences and therefore will play a vital role in this study. A SAS macro was developed to simulate longitudinal HRQoL data as seen in clinical trials with the capability of creating missing values based on different factors including the proportion of missing data, intermittent and monotone missing data patterns to approximate trial data with respect to deaths and withdrawals, relative frequency of these patterns, and more importantly, missingness mechanism.[3,4] A first-order autoregressive covariance matrix was used where the correlation between HRQoL measures is assumed to decrease over time. Mean HRQoL data (KCCQ) and correlation between follow-up data within patients across time used in the simulation was based on peer-reviewed articles and expert opinion.[5,6] Data for two treatment groups with equal number of patients was simulated in this study.

Methods

The variables included in the random-effects growth curve models include time (baseline, 30-days, 6-months, 1-year etc.), treatment, and interactions between treatment and time. Because follow-up QoL measurements are almost always strongly correlated with the baseline values, the model is adjusted for baseline QoL score. The intercept and linear effects of time are estimated using both fixed and random effects with an unstructured covariance matrix. Quadratic and cubic effects of time, and corresponding interactions with treatment, are screened for in the modeling process, and retained in the model if $p<0.05$, However, these effects are modeled as fixed effects only, to avoid over-parameterization[2]. The modeling process begins with the fitting of the full model, including quadratic and cubic effects of time and all time-by-treatment interactions, followed by a backwards stepwise process of eliminating terms in the model, beginning with

the cubic time-by-treatment interaction, the cubic time effect, the quadratic time-by-treatment interaction, etc. using a $p<0.05$ as the cutoff for inclusion in the model. If no time by treatment interaction is statistically significant at $p<0.05$, estimates of an overall treatment effect, across all time points, are derived from a model that includes treatment and time (including possible non-linear effects) only. Random-effects models give unbiased results in case of MAR. Parameters are estimated using the *restricted maximum likelihood (REML)* method, which is based on the Newton–Raphson algorithm. A two-tailed P-value of <0.05 was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) using PROC GLM for analysis of covariance and PROC MIXED for random-effects growth curve models[6]. Results from analysis of covariance and growth curve models are presented as mean (95% CI), and unmodeled data (raw means) is expressed as mean ± std.

Results

Table 1 lists a summary of parameters used in the simulation study. The QoL compliance summary of the simulated dataset with 8 timepoints and data through 5 years is shown in Table 2. Results from two separate growth curve models on the same dataset, one including quadratic effects of time (QUAD), and another including quadratic and cubic effects of time (CUB) are shown in Table 4. These models are run on 5 datasets, one each for data from years 1-5. Based on the simulated dataset, there is a sharp increase in QoL score in group A compared to a relatively smaller increase in group B at 1 month leading to a statistically significant difference (p-value<0.0001) that is reflected in both analysis of covariance and growth curve models. While there were no significant QoL differences between treatment groups at any follow-up timepoints beyond 1 month in the ANC model (Table 3), the inference from growth curve modeling depends not only on whether a QUAD or CUB model is fit, but also on the number of timepoints in the QoL dataset. While the mean difference in health score at 6 months in the year-2 dataset is significant in the QUAD model, there is no difference detected in the CUB model. Finally, in the analysis of full 5-year dataset, there is a statistically significant difference in QoL scores at 1,6, and 12 months using the QUAD model, but no such difference exists in the CUB model.

Table 1 Summary of parameters used in the simulation study

Parameters	Values
Number of timepoints	8
Timing of measurements of the outcome variable	Baseline; 1 month; 6 months; 1 year; 2 years; 3 years; 4 years; 5 years
Number of patients	Total N=800; 400 in each treatment group
Missing data mechanism	Missing at Random (MAR)
Percentage (%) of missing data at each timepoint	Treatment group A: 5; 35; 20; 20; 25; 30; 30; 40 Treatment group B: 15; 50; 30; 30; 30; 30; 25; 35
Mean HRQoL (mean±std)	Treatment Baseline 1M 6M 1Y 2Y 3Y 4Y 5Y A (N=400) 47±23 66±24 72±22 72±22 72±22 67±24 68±24 67±21 B (N=400) 47±22 52±25 71±22 71±22 67±23 70±22 68±21 66±20
Correlation between HRQoL measures	0.5

Table 2 Compliance summary of the simulated dataset

	A (N=400)			B (N=400)		
Visit	**# observed**	**# eligible**	**% with available data**	**# observed**	**# eligible**	**% with available data**
Baseline	380	400	95	338	400	85
1 Month	246	376	65	179	346	52
6 Months	277	355	78	217	306	71
1 Year	255	329	78	201	284	71
2 Years	221	298	74	167	236	71
3 Years	168	249	67	137	195	70
4 Years	145	204	71	128	163	79
5 Years	102	161	63	91	134	68

Table 3 Comparison of mean scores over time from analysis of covariance, adjusting for baseline QoL score

Time (months)	Raw means –A	Raw means - B	ANC-A	ANC-B	Mean difference (A-B) 95% CI	P-Value
1	64.9±21.7 (246)	50.8±22.8 (179)	65.0 (62.3, 67.8)	50.7 (47.4, 53.9)	14.4 (10.1, 18.6)	<0.0001
6	71.3±21.9 (277)	71.8±20.8 (217)	71.4 (69.0, 73.8)	71.7 (69.0, 74.4)	-0.4 (-4.0, 3.2)	0.8391
12	71.1±19.5 (255)	70.8±19.4 (201)	71.0 (68.7, 73.3)	71.0 (68.4, 73.6)	0.0 (-3.4, 3.5)	0.9820
24	73.5±19.6 (221)	68.1±21.2 (167)	73.7 (71.2, 76.2)	67.9 (64.9, 70.8)	5.8 (2.0, 9.7)	0.0032
36	69.9±20.1 (168)	73.0 ±17.6 (137)	69.9 (67.2, 72.6)	73.0 (70.0, 76.0)	-3.1 (-7.2, 0.9)	0.1301
48	69.6±20.6 (145)	66.9±19.9 (128)	69.3 (66.1, 72.5)	67.2 (63.9, 70.6)	2.1 (-2.6, 6.7)	0.3828
60	68.6±19.7 (102)	67.2±16.9 (91)	68.8 (65.3, 72.3)	67.0 (63.3, 70.7)	1.7 (-3.4, 6.8)	0.5054

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Table 4 Difference in QoL score between treatment groups over time using random-effects growth curve models

Model*	Time (months)	Raw means-A	Raw means-B	Raw means difference	GCM - A	GCM - B	GCM	GCM P-Value	AIC	BIC
							Predicted mean difference (A-B), 95%CI			
Year 1										
QUAD	1	64.9 ±21.7 (246)	50.8 ±22.8 (179)	14.1	64.7 (62.2, 67.2)	50.1 (47.2, 53.0)	14.6 (10.7, 18.5)	<0.0001	11958.7	11977
	6	71.3 ±21.9 (277)	71.8 ±20.8 (217)	-0.5	70.9 (68.5, 73.2)	71.6 (69.0, 74.3)	-0.8 (-4.3, 2.8)	0.6692		
	12	71.1 ±19.5 (255)	70.8 ±19.4 (201)	0.3	70.6 (68.2, 73.0)	70.8 (68.1, 73.5)	-0.2 (-3.8, 3.4)	0.9045		
CUB	1	64.9 ±21.7 (246)	50.8 ±22.8 (179)	14.1	Not enough data points to fit cubic effects of time					
	6	71.3 ±21.9 (277)	71.8 ±20.8 (217)	-0.5						
	12	71.1 ±19.5 (255)	70.8 ±19.4 (201)	0.3						
Year 2										
QUAD	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	65.6 (63.2, 68.1)	52.9 (50.1, 55.7)	12.7 (9.0, 16.4)	<0.0001	15265.2	15283.5
	6	71.3 ±21.9 (277)	71.8±20.8 (217)	-0.5	69.2 (67.2, 71.1)	66.2 (64.0, 68.4)	3.0 (0.1, 5.9)	0.0456		
	12	71.±19.5 (255)	70.8±19.4 (201)	0.3	71.8 (69.7, 74.0)	74.6 (72.1, 77.0)	-2.7 (-6.0, 0.5)	0.0979		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	72.1 (69.6, 74.6)	66.6 (63.7, 69.5)	5.5 (1.7, 9.3)	0.0048		
CUB	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	64.8 (62.3, 67.2)	50.0 (47.2, 52.9)	14.7 (10.9, 18.5)	<0.0001	15171.2	15189.5
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	70.9 (68.6, 73.2)	71.4 (68.8, 74.1)	-0.6 (-4.1, 2.9)	0.7543		
	12	71.±19.5 (255)	70.±19.4 (201)	0.3	70.5 (68.2, 72.9)	70.7 (68.1, 73.3)	-0.1 (-3.7, 3.4)	0.9363		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	72.3 (69.8, 74.8)	67.3 (64.5, 70.2)	5.0 (1.2, 8.8)	0.0099		
Year 3										
QUAD	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	65.8 (63.5, 68.1)	57.0 (54.3, 59.7)	8.8 (5.3, 12.3)	<0.0001	17889.7	17908
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	69.0 (67.1, 70.8)	63.7 (61.6, 65.8)	5.3 (2.4, 8.1)	0.0003		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	71.5 (69.6, 73.4)	69.6 (67.4, 71.7)	1.9 (-1.0, 4.9)	0.191		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	72.6 (70.5, 74.6)	74.1 (71.8, 76.4)	-1.5 (-4.6, 1.5)	0.3267		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	68.2 (65.5, 71.0)	69.1 (66.0, 72.1)	-0.8 (-4.9, 3.2)	0.6845		
CUB	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	65.4 (62.9, 67.8)	51.5 (48.7, 54.4)	13.8 (10.1, 17.5)	<0.0001	17743.9	17762.2
	6	71.3 ±21.9 (277)	71.8±20.8 (217)	-0.5	69.3 (67.3, 71.3)	67.8 (65.6, 70.0)	1.5 (-1.5, 4.5)	0.3109		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	71.9 (69.8, 73.9)	73.9 (71.6, 76.2)	-2.0 (-5.1, 1.1)	0.199		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	71.8 (69.5, 74.2)	66.0 (63.3, 68.7)	5.8 (2.2, 9.4)	0.0014		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	68.6 (65.8, 71.3)	72.5 (69.4, 75.5)	-3.9 (-8.0, 0.2)	0.0639		
Year 4										
QUAD	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	66.6 (64.4, 68.9)	58.2 (55.6, 60.8)	8.4 (5.0, 11.9)	<0.0001	20211.4	20229.7
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	68.7 (66.8, 70.6)	63.4 (61.3, 65.5)	5.3 (2.5, 8.1)	0.0002		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	70.5 (68.7, 72.4)	68.2 (66.2, 70.3)	2.3 (-0.4, 5.0)	0.0958		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	72.0 (70.0, 74.0)	73.3 (71.1, 75.5)	-1.3 (-4.2, 1.7)	0.4123		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	70.7 (68.6, 72.7)	72.2 (69.9, 74.5)	-1.6 (-4.6, 1.5)	0.3229		
	48	69.6±20.6 (145)	66.9±19.9 (128)	2.7	66.4 (63.4, 69.4)	65.0 (61.7, 68.3)	1.4 (-3.1, 5.9)	0.5379		
CUB	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	65.3 (62.9, 67.7)	54.3 (51.6, 57.1)	11.0 (7.3, 14.7)	<0.0001	20122	20140.2
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	69.4 (67.4, 71.3)	65.1 (63.0, 67.3)	4.2 (1.3, 7.1)	0.0042		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	71.9 (69.9, 73.9)	72.0 (69.8, 74.3)	-0.2 (-3.2, 2.9)	0.917		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	71.7 (69.7, 73.7)	72.5 (70.3, 74.8)	-0.8 (-3.8, 2.2)	0.5934		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	68.7 (66.2, 71.1)	66.6 (63.9, 69.3)	2.1 (-1.6, 5.8)	0.2656		
	48	69.6±20.6 (145)	66.9±19.9 (128)	2.7	67.6 (64.5, 70.8)	67.8 (64.5, 71.2)	-0.2 (-4.8, 4.4)	0.9367		
Year 5										
QUAD	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	67.1 (64.9, 69.3)	59.2 (56.7, 61.7)	7.9 (4.6, 11.2)	<0.0001	21857.1	21875.4
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	68.6 (66.8, 70.5)	63.3 (61.2, 65.4)	5.4 (2.6, 8.2)	0.0002		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	70.0 (68.3, 71.8)	67.2 (65.2, 69.2)	2.9 (0.2, 5.5)	0.0335		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	71.4 (69.5, 73.3)	71.9 (69.8, 74.1)	-0.5 (-3.4, 2.3)	0.7155		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	70.8 (68.8, 72.8)	72.6 (70.4, 74.8)	-1.7 (-4.7, 1.2)	0.2473		
	48	69.6±20.6 (145)	66.9±19.9 (128)	2.7	68.3 (66.1, 70.5)	69.0 (66.7, 71.4)	-0.8 (-4.0, 2.5)	0.632		
	60	68.6±19.7 (102)	67.2±16.9 (91)	1.4	63.8 (60.4, 67.1)	61.4 (57.9, 65.0)	2.3 (-2.5, 7.2)	0.344		
CUB	1	64.9±21.7 (246)	50.8±22.8 (179)	14.1	65.6 (63.3, 68.0)	55.5 (52.8, 58.2)	10.1 (6.6, 13.7)	<0.0001	21770.2	21788.5
	6	71.3±21.9 (277)	71.8±20.8 (217)	-0.5	69.1 (67.2, 71.0)	64.2 (62.1, 66.3)	4.8 (2.0, 7.7)	0.0008		
	12	71.1±19.5 (255)	70.8±19.4 (201)	0.3	71.5 (69.5, 73.4)	70.7 (68.5, 72.9)	0.8 (-2.1, 3.7)	0.5864		
	24	73.5±19.6 (221)	68.1±21.2 (167)	5.4	72.1 (70.1, 74.0)	73.7 (71.5, 75.9)	-1.6 (-4.5, 1.3)	0.27		
	36	69.9±20.1 (168)	73.0±17.6 (137)	-3.1	69.4 (67.3, 71.6)	69.3 (67.0, 71.7)	0.1 (-3.1, 3.2)	0.965		
	48	69.6±20.6 (145)	66.9±19.9 (128)	2.7	66.4 (64.0, 68.9)	64.5 (61.8, 67.2)	1.9 (-1.7, 5.5)	0.304		
	60	68.6 ±19.7 (102)	67.2 ±16.9 (91)	1.4	66.0 (62.5, 69.5)	66.2 (62.4, 69.9)	-0.2 (-5.3, 5.0)	0.9472		

QUAD and CUB refer to quadratic and cubic effects of time included as covariates in the growth curve models

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Discussion

There is statistically significant difference in QoL scores between treatment groups at 6 months and 1-year in models with quadratic time effects (Table 4), which is absent in the raw data and analysis of covariance model (Table 3) starting with datasets that contain follow-up scores at year 2 and beyond. Also, the between group differences at 1 month are much larger in the analysis of covariance model. It appears that the growth curves start to borrow too much information from the 1 month assessment resulting in some early QoL benefit seeming to carry over in to the 6 months and 1-year results. If the interest is in the earlier time points, there is no reason to fit a curve through the later time points. Even when a cubic term is added, the model is still being fit to describe the overall trend parsimoniously, and not to predict QoL score at each time point most accurately. The results show that the trajectory of QoL change over time is substantially altered after incorporating later time points and is probably unavoidable in the setting of growth curve modeling. This study aimed to demonstrate the issue of no consensus between two methods widely used in the analysis of HRQoL data.[7] Therefore, a thorough investigation into the choice of appropriate statistical methods to analyze data from quality-of-life studies in many different settings is needed.

Conclusion

Longitudinal random-effects growth curve models are widely used in analyzing HRQoL data in cardiovascular clinical trials. However, the choice of an appropriate statistical approach is vital because each dataset is different and applying same methods must be avoided to obtain accurate and meaningful results. Therefore, additional work is in progress to explore the impact of factors like the sample size, number and timing of the longitudinal timepoints, percentage of missing data and missing data patterns to provide a comprehensive guide on the use and optimality of statistical methods in the analysis of HRQoL data in cardiovascular clinical trials.

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Conflicts of interest

The authors declared that there are no conflicts of interest.

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