

Tools & Techniques: Analysis of clustered data in interventional cardiology: current practice and methodological advice

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Background

Clustered data are common in the field of interventional cardiology. Often multiple lesions are examined within the same patient and intravascular imaging modalities - such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) - result in multiple measurements from the same vessel segment. Multiple observations from one patient are likely to be correlated, which has implications for the statistical approach used to analyse the data.

The approach taken in the statistical analysis should be based on the study objectives. If we study the effect of medication versus no medication, the level of analysis should be the patient. If we study the effect of stent implantation, the level of analysis could be the stented segment. One patient can have multiple stented segments and these are likely to be correlated. Ignoring this correlation in the analysis leads to a too strong statistical inference. Specifically, misleadingly small standard errors (and thus p-values and confidence intervals) will be found when all observations are considered as independent. This wrongly inflates statistical power. Thus, analyses of data that include multiple observations per patient require some form of adjustment to account for the correlation between observations. This is common knowledge in the statistical literature (for example, Molenberghs¹). In the medical literature, however, clustered data are often analysed without taking the within-cluster correlation into account².

The aim of this paper is to review the current analytical approach to clustered data in the field of interventional cardiology; to present and illustrate statistical methods that take into account possible

correlation within clusters. We provide syntax for different statistical packages to allow researchers to apply these methods.

Current practice

We conducted a systematic review to gain insight in the current statistical approaches to clustered data in the field of interventional cardiology and focused on studies on optical coherence tomography (OCT), since this technique results in large numbers of observations per patient. We conducted a PubMed literature search for original studies published between January 1, 2012 and December 31, 2012 in six important (interventional) cardiology journals: *Circulation*, *Circulation Cardiovascular Interventions*, *EuroIntervention*, *European Heart Journal*, *Journal of the American College of Cardiology (JACC)* and *JACC Cardiovascular Interventions*. The search string “optical coherence tomography” yielded 25 potentially eligible studies. These were reviewed by two independent reviewers where, in case of disagreement, a third reviewer was consulted. Case reports, reviews and editorials were excluded, leaving 17 studies (**Online Appendix 1**) all reporting data derived from multiple observations per patient. In 15 (88%) of the 17 studies, inferences made from these multiple observations per patient were reported. Of those 15 studies, only five (33%) took the clustered nature of the data clearly into account in the statistical analysis. In three (20%) studies it was not clear whether the clustering was taken into account. In seven (46%) studies it was clear that the clustering within patients was not taken into account. In these studies t-tests were mostly conducted, which assume that all observations are independent.

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Methods to analyse clustered data

We illustrate the use of different statistical methods with data from a study that evaluated late recoil of a novel bioabsorbable everolimus-eluting coronary scaffold (BVS)³. The study consisted of 16 patients who were treated with elective BVS implantation. All patients underwent an IVUS examination post-procedure and at six-month follow-up. A total of 484 paired cross-sectional areas (CSAs) were acquired, on average over 30 per patient. Late absolute stent recoil was defined as stent area at post-procedure minus stent area at follow-up. In each CSA, plaque morphology was assessed qualitatively and classified as calcific, fibronectrotic, or fibrocellular plaque.

In these data we address two research questions with different methods in line with the reviewed literature.

Research question 1: What is the stent recoil in this population? We can hereto provide a mean with a 95% confidence interval (CI).

Research question 2: What is the difference in stent recoil between the three different plaque types? We can hereto provide differences between plaque types with 95% CI.

METHOD 1: INDEPENDENT OBSERVATIONS

The simplest method is to analyse the data at CSA level, without taking into account the clustering within patients. Formally this approach assumes that each observation is statistically independent, i.e., that there is no correlation between different CSAs from the same patient. We calculate mean absolute recoil and 95% confidence interval (95% CI) based on all 484 CSAs. Alternatively, the mean and 95% CI can be obtained from a linear regression model without any covariates. In this model only the intercept is estimated which equals the mean recoil. To estimate the differences between plaque types, a linear regression model with plaque type as a categorical covariate can be fitted. The linear models estimate unconditional effects, i.e., the average difference between plaque types in the population.

METHOD 2: CLUSTERED OBSERVATIONS

In contrast to the first approach, we can take the correlations between recoil values within patients into account. We can thereto use a linear multilevel model, also called random effects, mixed, or hierarchical model. The multilevel model contains two levels: patient and CSA. The patient is included in the model as a random effect, which allows estimation of patient-specific recoil values.

The estimated intercept equals the mean recoil, with clustering taken into account.

To estimate the differences between plaque types we used a linear multilevel model with a random intercept for patient and plaque type as a categorical covariate.

The interpretation of the differences between plaque types is somewhat different than in method 1. In method 1, we estimate differences within and across patients, while in method 2, we strictly estimate differences within patients.

METHOD 3: PATIENT LEVEL

Another approach simply averages the recoil values per patient. These means are saved. In a second step, the means are averaged to obtain an overall mean over all observations.

Results

All three methods estimated a very similar mean absolute recoil of about 0.65 to 0.66 mm² (**Table 1**). As expected, the 95% confidence interval of the absolute recoil was smallest (−0.80; −0.49) when all CSAs were analysed as independent observations and largest (−1.32; −0.01) when the CSAs were first summarised per patient. When the CSAs were analysed as clustered observations with a multilevel model, the 95% CI was −1.27 mm² to −0.05 mm², which is clearly larger than the 95% CI obtained with method 1, and close to the width obtained with method 3.

When estimated with a naïve linear model, ignoring clustering, the mean recoil per plaque type was −0.74 mm² in fibro-cellular, −0.20 mm² in calcific, and −1.03 in fibro-necrotic plaques. The corresponding differences (95% confidence interval) were 0.54 mm² (0.19; 0.89) for fibro-cellular vs. calcific plaques and −0.29 mm² (−0.66; 0.09) for fibro-cellular vs. fibro-necrotic plaques (**Table 2**). When clustering was taken into account in the multilevel model, the differences were 0.60 mm² (0.21; 1.00) and −0.06 mm² (−0.38; 0.26), respectively. This difference could be explained by the fact that the multilevel model estimates conditional, or within patient differences. When all CSAs are considered independent, fibro-necrotic plaques have 0.29 mm² less recoil than fibro-cellular plaques. However, when we acknowledge that CSAs are clustered within patients, this difference almost disappeared (0.06 mm² less recoil). In this example the 29 mm² absolute recoil difference is contributed to a high or low recoil level in some patients, instead of to the plaque type itself. Within a patient, fibro-cellular plaques appear to give no more recoil than calcific plaques.

Table 1. Methods for estimating mean recoil in total population (n, CSA=484; n, patients=16).

Method	Clustering taken into account?	Statistical method	Level	Mean recoil (95% CI)
Use all CSAs as independent observations	No	Calculate mean+se/95% CI; linear regression with one common intercept	CSA	−0.65 (−0.80; −0.49)
Use all CSAs as clustered observations	Yes	Multilevel linear regression	CSA	−0.66 (−1.27; −0.05)
Summarise CSAs per patients	Yes	Calculate mean+se/95% CI; linear regression with one common intercept	Patient	−0.66 (−1.32; −0.01)

See Online Appendix 2 for syntax for presented methods.

Table 2. Methods for difference in recoil between plaque types (n, CSA=484; n, patients=16).

Method	Clustering taken into account?	Statistical method	Level	Difference between plaque types (95% CI)
Use all CSAs as independent observations	No	Linear regression	CSA	0.54 (0.19; 0.89)* -0.29 (-0.66; 0.09)**
Use all CSAs as clustered observations	Yes	Multilevel linear regression	CSA	0.60 (0.21; 1.00)* -0.06 (-0.38; 0.26)**

* Difference between fibro-cellular (reference) and calcific plaques; ** Difference between fibro-cellular (reference) and fibro-necrotic plaques. See Online Appendix 2 for syntax for presented methods.

In this particular example the estimated mean recoil in the overall population was not largely affected by using a multilevel model; only the confidence interval increased. The estimated difference between plaque types was however affected. The difference between fibro-cellular and calcific plaques was only borderline significant in the multilevel model.

In general, the change in point estimates between naïve models and multilevel models will be influenced by the correlation within patients, and the difference in number of observations between patients. When both are small, point estimates are likely to be very similar between the methods. However, the standard error and confidence intervals will generally increase, and corresponding p-values decrease when using a multilevel model. Ignoring clustering using naïve models will exaggerate statistical significance.

Conclusion and recommendations

According to literature review, the current analytical approach to clustered data in the field of interventional cardiology, specifically OCT, is suboptimal. A large number of studies ignored the clustered nature of their data, or it was unclear which statistical methods were used. If we assume that observations within one patient are correlated, ignoring clustering may lead to wrong conclusions.

Our data example shows that indeed misleadingly small confidence intervals can be estimated with standard linear regression. The third method – summarising CSAs per patient – is statistically correct when analyses on patient level are performed, but inefficient.

When observations within patients are not correlated, the clustering can theoretically be ignored. However, this is clinically unlikely

and, in the absence of correlation, the results from standard and multilevel analysis will be the same. We therefore recommend to always use multilevel models when analysing multiple observations per patient, to make correct statistical inferences and not inflate statistical power. These models are now widely available in statistical software, and syntax is provided in **Online Appendix 2**.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Online data supplement

Online Appendix 1. Fifteen studies with inference based on clustered data; five clearly analysed taking structure into account.

Online Appendix 2. Syntax code for the performed analyses in SPSS, SAS and R.