Letter to the Editor

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Comment on "Modeling the Growth of Infrarenal Abdominal Aortic Aneurysms" by Bailey et al.

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Dear Editor:

The authors [1] have provided some interesting results and furthered understanding of the statistical challenges and appropriate procedures for estimating aneurysm growth rates. We have learned a great deal from this study and applaud their efforts. But after reviewing their study carefully, we feel that an exponential modeling approach, as applied in some previous research [2,3], is preferable because it models a more realistic pattern of aneurysm growth, in which growth depends not only on duration but on initial aneurysm size. The exponential model posits that the last measured aneurysm size, A_l, and the first measured size, A_f, are related as follows: (1)

$$A_l = A_f e^{\beta T}, \quad (1)$$

where T = the time between the first and last tests and β is a coefficient to be estimated. This approach is implemented by taking the natural logarithm of both sides of Equation 1 and then estimating by ordinary least squares (OLS), allowing for no intercept term. This functional relationship has the properties that aneurysm growth is larger, the greater the initial aneurysm size and the longer the patient is followed.

One criticism of this approach is that it does not use all available data, such as when patients have more than two imaging studies. But if patients have several measured sizes, one may still apply this method, taking advantage of these multiple measurements to enlarge the sample size. Suppose, for example, that there are three measured sizes for the same patient and that we also know the dates for each measurement. One can then obtain two observations for this patient. The first observation relates the difference between the 1st and 2nd size to the time between the first and second tests, while the second relates the difference between the 2nd and 3rd size to the time between the second and third tests. For the first observation, the first size can be regarded as A_f and the second size can be regarded as A_l, where T is the time between the first and second tests according to Equation 1 above. For the second observation, the second size can be regarded as A_f and the third size can be regarded as A_l, where T is the time between the second and third tests. However, this modeling approach may suffer from the fact that the *same* patient appears in the data set more than once (Gujarati and Porter 2009). The error terms in the linear regression will then be correlated because several error terms are from the same patient. A model clustering the error terms and controlling for autocorrelation should be applied. Clustering the error terms enables us to control for the correlations between several error terms from the same patients. Autocorrelation occurs because the different observations from the same patients are also correlated. For example, the size difference for the first observation is correlated with that of the second observation from the same patient. This approach using all available data increases statistical power and precision of the estimates. However, it may exacerbate selection effects. For example, if patients with multiple imaging studies tend to have stable, slow-growing aneurysms while fast-growing aneurysm patients are selected out for surgery after fewer imaging studies, this approach will overweight the slow-growing aneurysms, biasing growth estimates downward.

In prior correspondence, the authors have argued that the exponential model is no better than the OLS estimates they provided and which they considered to be inferior to their preferred models; namely, the linear multilevel model (MLM) and quadratic MLM models. The authors also noted that they estimated the exponential model, finding that for a person with a 1 cm aneurysm, the annual growth would be 0.052 cm, increasing to 0.088 cm after 10 years. However, this example is misleading because it uses patients with aneurysm sizes that were not in the database. To be enrolled in their study, patients had to

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have an initial aneurysm size ≥ 3 cm or 1.5 times the size of the adjacent aorta. It seems doubtful that more than a few, if any, patients with an aorta = 1 cm were included in the analysis. It would be more reasonable and informative to apply aneurysm sizes actually observed in the data to the exponential model estimates.

When one does this, their results using the exponential model indicate the following:

Initial Aneurysm Size	*Annual Growth*
3 cm	0.16 cm
4 cm	0.21 cm
5 cm	0.26 cm
5.5 cm	0.29 cm

These growth rates are consistent with the values in their preferred models; namely, the MLM linear and MLM quadratic models. But, unlike their models, the exponential approach shows that growth increases as the aneurysm size is greater, which we believe makes compelling clinical and anatomical sense. Their MLM linear model concludes that growth is the same regardless of aneurysm size, while the MLM quadratic model estimates that growth actually declines over time as the aneurysm is increasing in size. We find this implausible and believe it may just be tracking a selection effect in the data, e.g., patients with large unstable aneurysms are differentially selected out for surgery, leaving a disproportionate share of large aneurysm patients whose aneurysms are more stable.

The authors do not include further imaging studies once a patient has an imaging study that measures the aorta as being ≥ 5.5 cm. They note that this is because growth of large aneurysms may be different. We concur and, in fact, their statement on this point is really an admission that aneurysm growth does depend on aneurysm size, most probably with larger aneurysms growing faster. But none of their models capture this effect. The exponential modeling approach does.

The authors' decision to exclude further imaging studies once patients have passed the size threshold for intervention may, however, be justifiable on the grounds that it mitigates selection effects. If patients with large unstable aneurysms are differentially selected out for surgery, including the remaining large stable aneurysms in the study may exacerbate selection effects, and one might erroneously estimate that larger aneurysms grow more slowly. While statistical methods for dealing with selection effects are well known in the literature [4], this would require estimating an equation predicting the probability that a patient is selected out for surgery in addition to estimating growth. The data requirements to implement this selection correction, both in terms of sample size and variables needed, can be quite formidable.

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