Analysis of Coronary Artery Calcification Data: Modeling Considerations

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Tea Time for Science
4/11/2011

Presentation Outline

1. Coronary Heart / Artery Disease
2. Coronary Artery Calcification
3. Analysis Methods
4. Simulation Study
5. Real Example and Results
6. Conclusions and Further work

The Disease

Coronary Heart / Artery Disease

The Disease

Coronary Artery Disease (CAD) is the leading cause of death in the US for both Men and women (NHLBI, 2009).

CAD is caused when the arteries that supply the heart with oxygenated blood become blocked by Plaque

This condition is often referred to as *Atherosclerosis* and over time, can lead to heart attack, stroke, and death

Coronary Artery Calcification

The Disease

Atherosclerosis is caused when the inner lining of the arteries, specifically the endothelium, are injured or damaged.

Blood cells clump at the injury site in an attempt to repair the vessel wall, this leads to inflammation.

Plaques are then deposited on the artery wall and will continue to build over time.

These build ups rupture and harden over time and block the flow of blood.

Coronary Heart / Artery Disease

The Disease

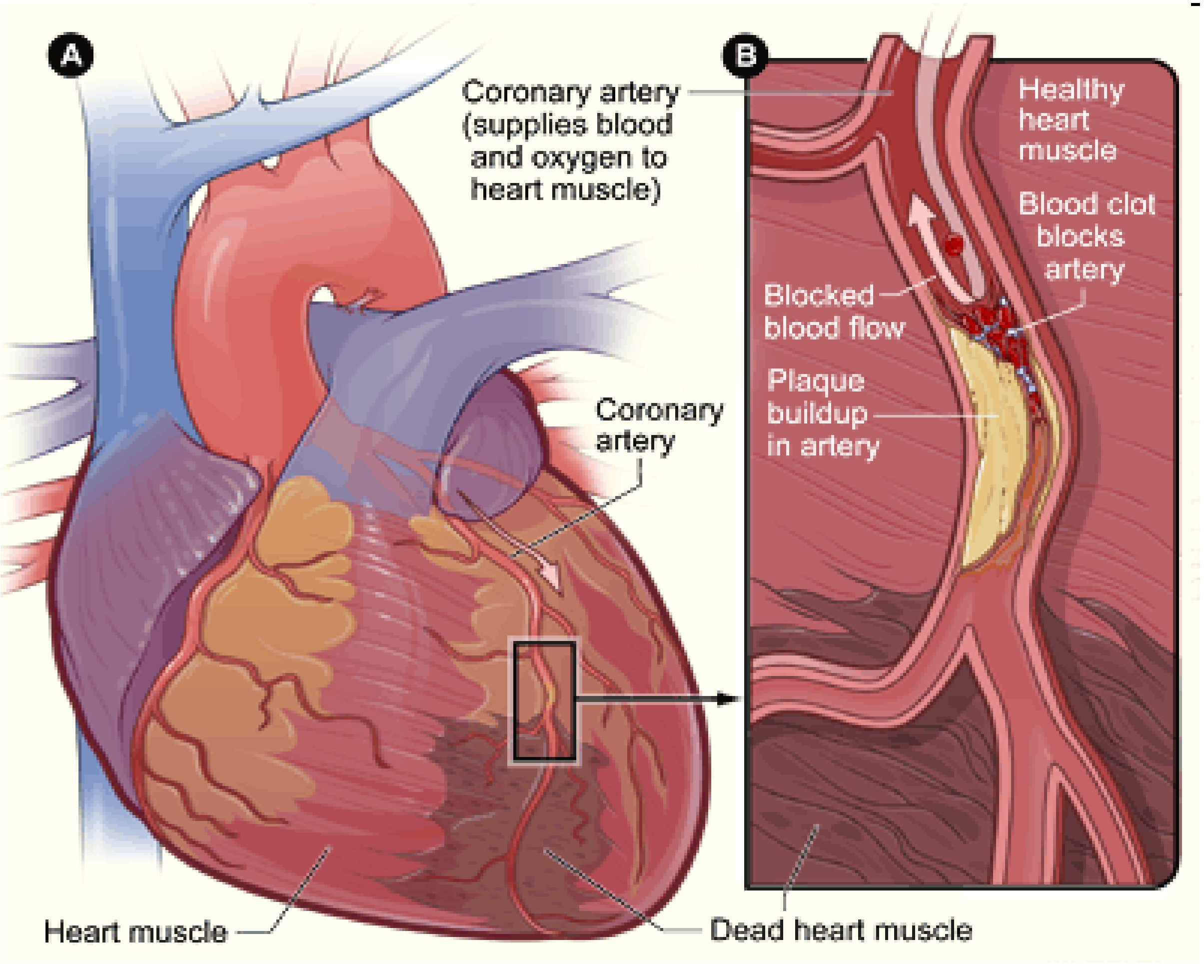


Image Courtesy of NHLBI

Coronary Heart / Artery Disease

The Disease

There are many factors that are linked to the development of Atherosclerosis (smoking, diet etc..).

Atherosclerosis is usually symptom free until severe blockages are present.

Early detection of coronary artery calcification (CAC) and narrowing is key to prevention of later events.

CAC has been shown to be an independent risk factor for cardiovascular events (Budoff et al, JACC 2007; Raggi et al, JACC 2004, Greenland et al, JAMA 2004).

Coronary Artery Calcification

Measurement of CAC

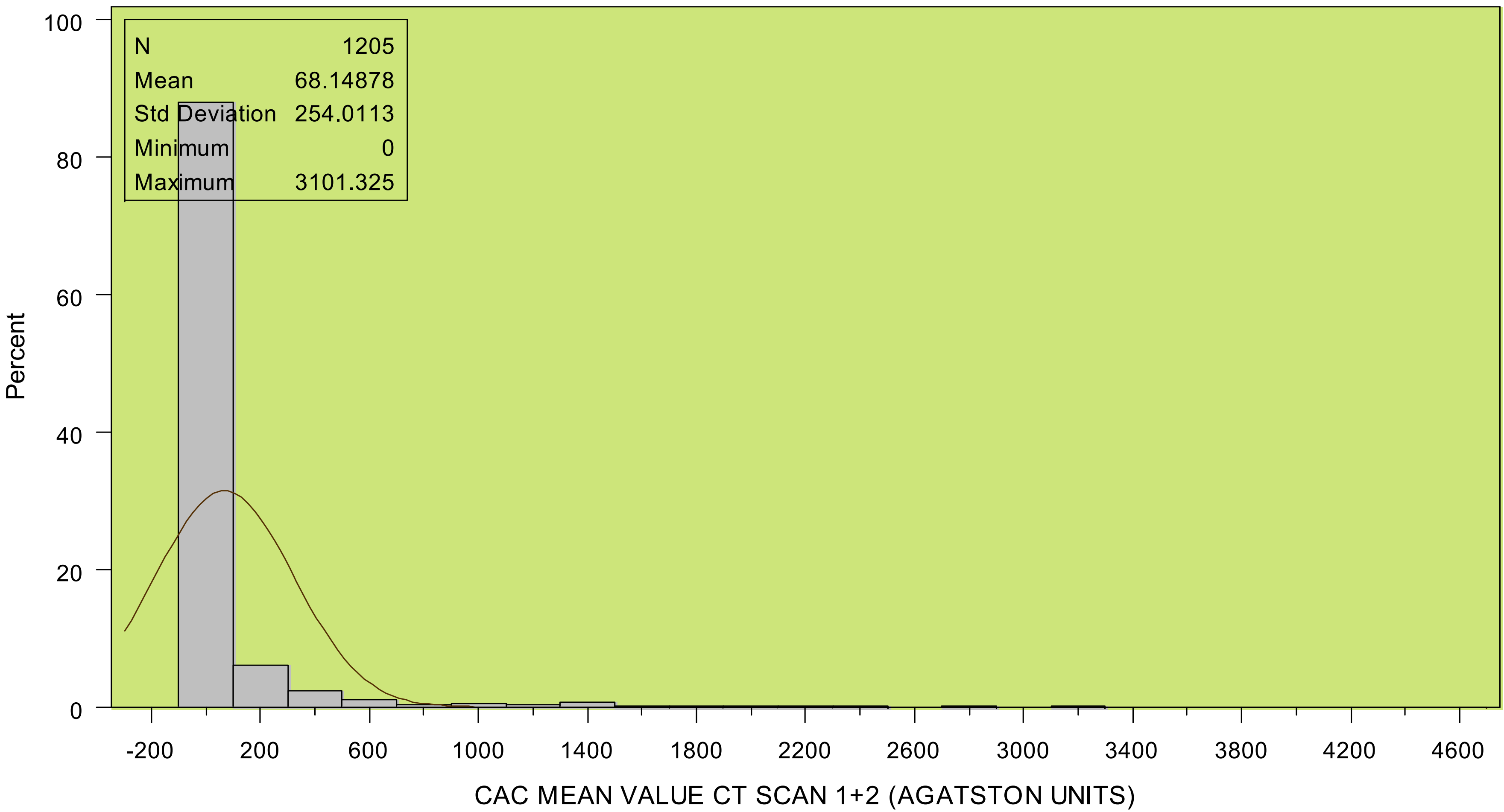
Ultra fast CT is used to detect and quantify CAC levels.

Measurements are usually given in AS (Agatston units), however it is sometimes measured as a volume (mm^3), or mass scores (Agatston, 1990).

Agatston Score measures the area of the plaque multiplied by some density factor. Scores can range from 0 to several thousand.

Coronary Artery Calcification

CAC Scores



Coronary Artery Calcification

CAC Scores

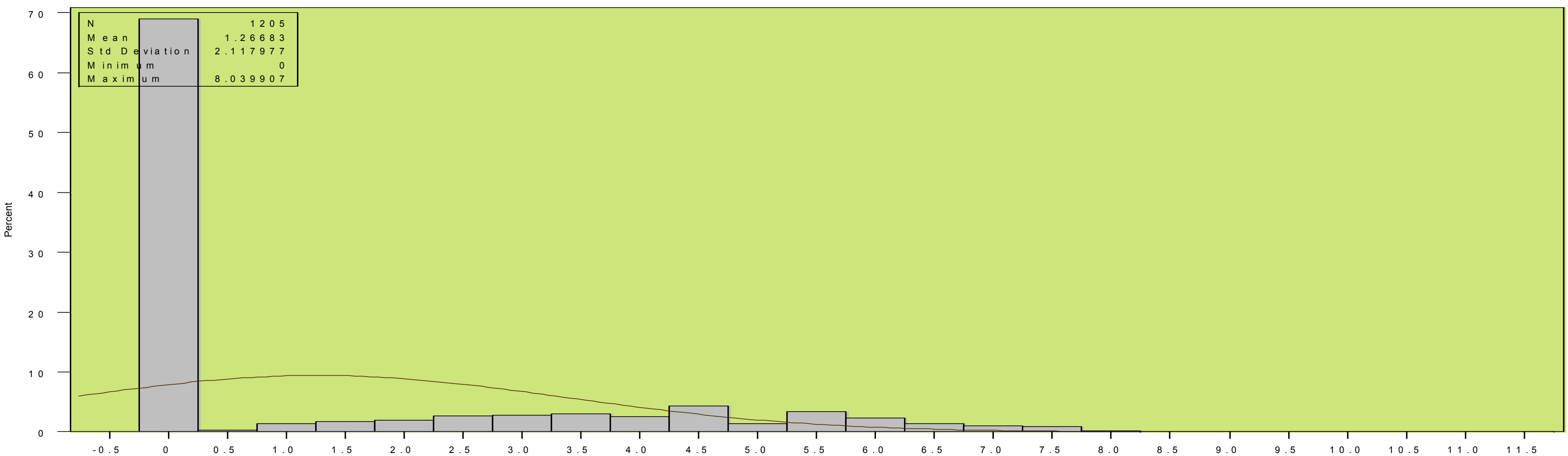
As you can see from the previous figure that raw CAC scores have a very high prevalence of 0 scores.

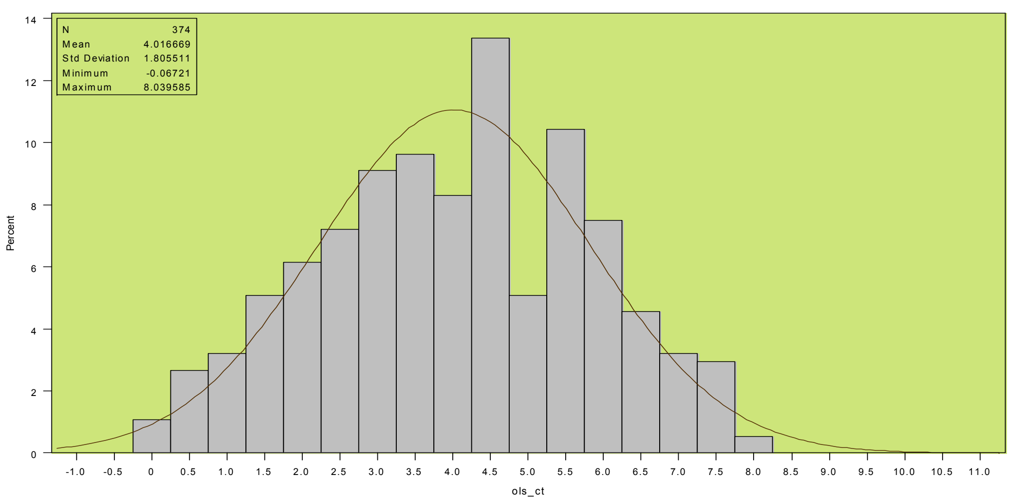
CAC scores are also notorious for being highly right skewed.

Historically, log(CAC+1) and Log(CAC) where CAC>0 have been used to facilitate linear regression techniques.

Other methods have also been implemented to assist in analysis and interpretation of CAC data.

Coronary Artery Calcification





The data above represents the distribution of log(CAC+1)…

while the data to the left is only the portion with measureable CAC

Current Analytic Methods

Analysis Methods

Analytic Challenges associated with CAC data.

Immeasurable CAC is present in many subjects and is represented by some lower bound (usually zero).

Large scores tend to violate many analytic assumptions.

Ordinary least squares regression analysis may be inappropriate and limited dependent variable data analysis can be complex and difficult to interpret

Analysis Methods

Analytic Methods associated with CAC data.

1. Linear Regression
2. Restricted Linear Regression
3. Binary Logistic Regression
4. Multinomial Logistic Regression
5. Tobit Limited Dependent Regression

Analysis Methods
Linear Regression

Linear regression model and assumptions

$$y = \alpha + \beta x + \varepsilon$$

Linear Regression assumptions:

- Linear Relationship between x and y
- Independence of observations
- Normality of the error distribution~N(0,σ^2)
- Homoscedasticity

Analysis Methods
Linear Regression

Why use linear regression

Estimates are easily interpreted and understood by clinicians.

Small sample sizes can be used.

Effect sizes are easily obtained

Analysis Methods
Linear Regression

Why not to use linear regression

Censored data tends to produce inconsistent parameter estimates.

Estimation is sensitive to the normality of the error terms.

Deviations from normality and linearity can add substantial error to parameter estimates.

Non uniform variance due to censoring will cause standard error estimates to be either too small or too large.

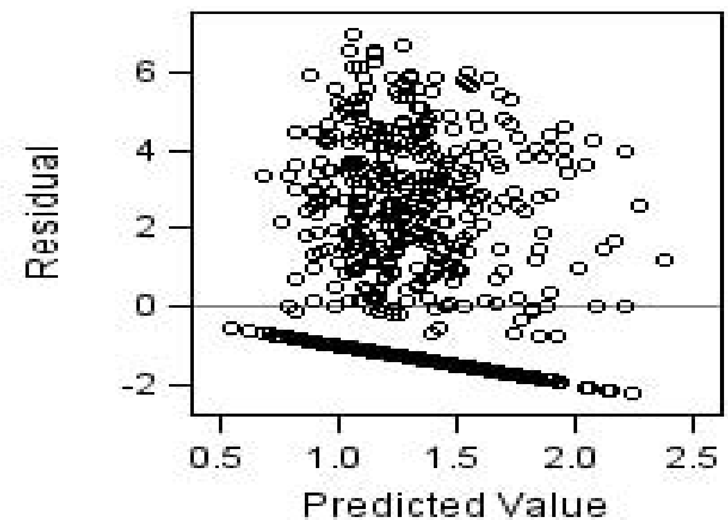
Analysis Methods
Linear Regression

Linear Regression assumptions

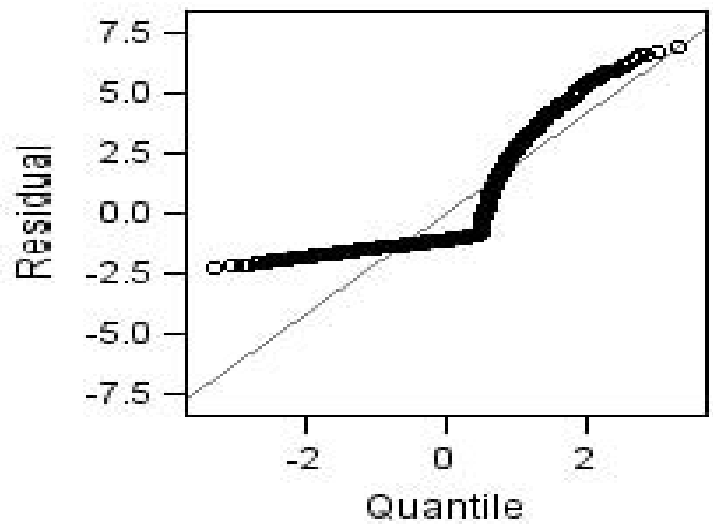
Linear Relationship between x and y:

there may be a linear relationship between observed CAC and the predictor, but not when the censored values are included

Constant error variance

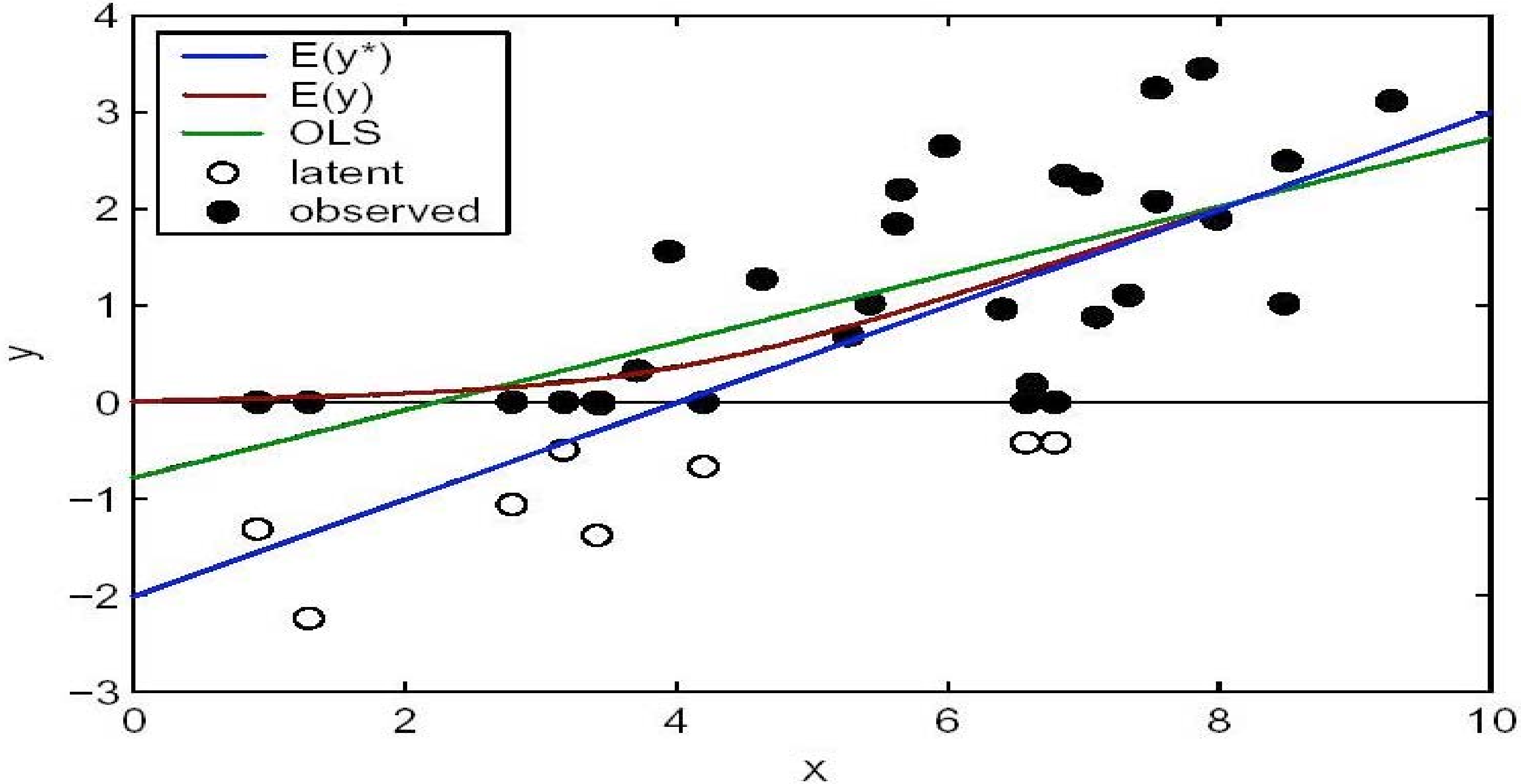


Normality of the error



Analysis Methods
Linear Regression

Linear Regression Bias



Graciously borrowed from David Madigan's web page

http://www.stat.columbia.edu/~madigan/G6101/notes/logisticTobit.pdf

Analysis Methods
Restricted Linear Regression

Why don't we just analyze the data that has measureable CAC values?

$$y = \alpha + \beta x + \varepsilon \;\; where \; y \neq 0$$

We may satisfy the assumptions for linear regression analysis, but in most cases, 30-60 % of subjects have non measureable CAC.

Excluding these data points may add significant bias to the parameter estimates found in the model.

Analysis Methods
Logistic Regression

Logistic regression model and assumptions

$$logit\left[\pi(x)\right] = \log\left(\frac{\pi(x)}{1-\pi(x)}\right) = \alpha + \beta x$$

$$\pi(x) = \frac{e^{(\alpha+\beta x)}}{1-e^{(\alpha+\beta x)}} \qquad Odds\,of\;CAC > 0 = \frac{\pi(x)}{1-\pi(x)} = e^{\alpha}(e^{\beta})^{x}$$

$$Thus\;\;OR = e^{\beta}$$

Logistic Regression Assumptions:

Underlying distribution is binary
Independence of observations
linearity between IV's and the Log odds
Small sample sizes can produce poor power

Hosmer and Lemeshow (2000) recommend at least n=400

Analysis Methods
Logistic Regression

Why Use Logistic Regression?

The error terms do not have to be normally distributed

The relationship between X and Y does not have to be linear

There is no homogeneity of variance assumption

Analysis Methods
Logistic Regression

Why Not Use Logistic Regression?

Dichotomization can be harmful to estimation and hypothesis testing (Federov et al, 2009).

This leads to a loss of information/power and increased sample sizes to detect true effects.

If there is a non-linear effect, splitting the data will not allow detecting this relationship.

Requires much more data than OLS Regression, loss of information will cause an increase in sample size to maintain power.

Analysis Methods
Logistic Regression

Why Not Use Logistic Regression?

When the study is prospective; the incidence of measureable CAC is high and thus the odds ratio is an overestimate relative risk.

However, some have argued that since the distribution of CAC scores does not follow a known distribution, the information lost is minimal and the ease of results presentation makes up for the loss.

Analysis Methods
Multinomial / Ordinal Logistic Regression

Common classifications of CAC data

Reduce the continuous outcome CAC data to binary or ordinal response.

Some popular categorizations of CAC data…

Measureable (>0) vs. non measureable CAC (0)

Low CAC (≤10) vs. high CAC (>10)

Categories: 0, 0-10, 11-99, 100-399, 400-infinity

Have seen data driven cut points, but they are not recommended.

Analysis Methods
OLS and Logistic Regression

Problems with the approaches?

OLS regression is clearly inadequate in handling data with clustering at zero.

Binary regression models (logit, probit, LPM) are adequate if you are interested only in the probability of limit vs. non-limit responses. They fail to extract all of the information available.

Ordinal regression models with arbitrary cut points can be, but are rarely fully efficient.

Tobin (1958) proposed a latent model approach to deal with the zeros.

Analysis Methods

Truncated v Censored

Truncated: value is incomplete due to the selection process of the study. Usually occurs when both the dependent and independent variables are lost.

Censored: value is incomplete due to random factors for each subject. Usually occurs when data on the dependent variable is lost but not the independent variables. May be due to top / bottom coding.

Analysis Methods
Tobit Limited Dependent Regression

For left censored data, censored at y_0.

$$y^* = \alpha + \beta x + \varepsilon \qquad \varepsilon \sim N(0, \sigma)$$

$$y = \begin{Bmatrix} y^* & if\ y^* > y_0 \\ 0 & if\ y^* \le y_0 \end{Bmatrix}$$

The Tobit regression model assumes that the underlying dependent variable has negative values that are censored at zero. However, it is routinely used when observed values are clustered at zero, irrespective of censoring. (Sigelman and Zeng, 1999)

Analysis Methods
Tobit Math Stuff

The log-likelihood function for the Tobit model when y_0=0:

$$\ln L = \sum_{i=1}^{N} \left\{ d_i \left(-\ln\sigma + \ln\phi\left(\frac{y_i - X_i\beta}{\sigma}\right)\right) + (1-d_i)\ln\left(1-\Phi\left(\frac{X_i\beta}{\sigma}\right)\right)\right\}$$

There are two parts to the log-likelihood function.

Part 1:

$$d_i \left(-\ln\sigma + \ln\phi\left(\frac{y_i - X_i\beta}{\sigma}\right)\right)$$

This corresponds to the classical regression of uncensored variables.

Part 2:

$$(1-d_i)\ln\left(1-\Phi\left(\frac{X_i\beta}{\sigma}\right)\right)$$

This corresponds to the relevant probabilities that an observation is censored.

Analysis Methods
Tobit Math Stuff

The log-likelihood of the Tobit model is the sum of the log-likelihoods for each observation.

The Tobit model weights censored and uncensored values differently because of the log-likelihood function.

The Tobit model observes the censored values, but places more weight on the uncensored values for a more accurate estimate.

The OLS will weight every value equally, resulting in a poor model.

Analysis Methods
Tobit Limited Dependent Regression

For CAC data, the Tobit model assumes that our data is censored at zero but may continue onto the negative scale if uncensored.

How can that be, an individual cannot have negative calcification? Can they?

No. But the distribution of CAC is a lognormal type and is transformed to conform to the assumptions of the model. When done, all of the CAC values less than 1 become negative log(CAC) values. So log(CAC) can take values that are negative. Note: log (CAC+1) values are always positive.

Analysis Methods
Tobit Limited Dependent Regression

Why Use the Tobit Model

Handles the point mass zeros and the continuous data while producing a single parameter estimates.

Using OLS regression techniques will lead to downward biased and inconsistent parameter estimates.

Can be applied in most statistical software programs.

Analysis Methods
Tobit Limited Dependent Regression

Why Not Use the Tobit Model

The Tobit censored regression model assumes that the error distribution of the underlying data is normal and is sensitive to violations of this assumption.

Heteroskedastic errors can lead to biased estimates where the OLS violation leads to underestimated standard errors.

Must graphically examine data to verify errors are i.i.d. normal.

Analysis Methods
Generally accepted interpretation of Parameter Estimates

Linear Regression: For a one unit change in the independent variable X, there is a $\widehat{\beta}$ unit change in the dependent variable Y.

Restricted Linear Regression: For a one unit change in X, there is a $\widehat{\beta}$ unit change in Y when Y>0.

Binary Logistic Regression: For a one unit change in X, there is a $\widehat{\beta}$ unit change in the log odds of $Y_{binary}=1$ ***<u>or</u>*** for a one unit increase in X, the odds of $Y_{binary}=1$ increases by a factor of $e^{\widehat{\beta}}$.

Ordinal Logistic Regression: For a one unit change in X, there is a $\widehat{\beta}$ unit change in the log odds of $Y_{ordinal}$ being "higher".

Analysis Methods
Interpretation of Parameter Estimates

Tobit Censored Regression Model

Recall that in OLS there is only one conditional mean function

$$\partial E(y) / \partial x_k = \beta_k$$

The Tobit model has 3 conditional means (Greene, 1997)…

1. those of the latent variable y*

$$\partial E(y^* \mid x) / \partial x = \beta$$

2. those of the observed dependent variable y

$$\partial E(y \mid x) / \partial x = \beta \, \Phi\left(\frac{x\beta}{\sigma}\right)$$

Estimated probability of observing an uncensored event

Analysis Methods
Interpretation of Parameter Estimates

Tobit Censored Regression Model

The Tobit model has 3 conditional means (Greene, 1997)…

3. those of the uncensored observed dependent variable y

$$\partial E(y \mid y > 0, x) / \partial x = \beta(1 - \delta\left(-\frac{x\beta}{\sigma}\right))$$

Where

$$\delta(\alpha) = \lambda(\alpha)(\lambda(\alpha) - 1)$$

$$\lambda(\alpha) = \phi(\alpha) / (1 - \Phi(\alpha))$$

$$\alpha = \left(\frac{x\beta}{\sigma}\right)$$

Analysis Methods
Interpretation of Parameter Estimates

Tobit Censored Regression Model

In most cases, software returns β and is interpreted as the change in x and its effect on y^*.

<u>RECALL:</u> we are analyzing the logarithm of CAC, thus the parameter estimates of the linear regression models are the difference in logarithms ≈ logarithm of the ratio. We can exponentiate the estimate and CI and recover the ratio of geometric means which is roughly interpreted as the multiplicative increase in the true distribution of CAC for every unit change in the independent variable.

Simulation Study

Simulation Study

The Goal of the simulation study is not to make statements based on the true distribution of CAC, rather to compare the performance of different analysis techniques with censored data.

In the study, the data is modeled such that the Tobit Censored regression model is correctly specified. The distribution of CAC conditioned on the covariates was normal with a uniform variance.

However, under normal conditions, CAC data may not have the properties desired.

Simulation Study

Monte Carlo simulation done with 1000 samples sets of 1000 observations each…

$$\log y^* = \alpha + \beta x + \varepsilon$$

$$\varepsilon \sim N(0,1) \quad x \sim N(100, 4)$$

The relationship between x and log y is set to a known value of β = 1.0.*

Three different censoring patterns were examined, 25% left censored, 50% left censored, and 65% left censored.

Simulation Study

The sample mean parameter estimates were noted and confidence intervals were calculated at the 2.5 and 97.5 percentiles

	Continuous Models			Categorical Models	
Modeled Censoring	OLS Proc GLM	OLS (restricted) Proc GLM	Tobit Proc QLIM/LIFEREG	Binary Logistic Proc Logistic	Prop Odds Logistic Proc Logistic
25% left Censored	0.750 (0.717-0.783)	0.951 (0.927-0.975)	1.000 (0.978-1.023)	1.828 (1.562-2.181)	1.792 (1.662-1.935)
50% left Censored	0.499 (0.466-0.534)	0.906 (0.872-0.941)	0.999 (0.971-1.032)	1.821 (1.569-2.106)	1.799 (1.644-1.969)
65% left Censored	0.350 (0.317-0.383)	0.874 (0.827-0.922)	1.001 (0.962-1.044)	1.819 (1.567-2.137)	1.812(1.648-2.008)

$OLS_{\beta} \approx \beta - (OLS_{Bias} \times \beta)$ When assumptions are met

Simulation Study

What if the data assumptions are not met?

Austin et al (2000) presented a simulation study that compared OLS to Tobit regression in the presence of non normal error terms and non constant error variance.

When the Tobit model is correctly specified, the relative bias in the parameter estimate is close to 0 while the bias in the OLS model is proportional to % of censored observations.

When the conditional distribution is the mixture of 2 normal distributions, the bias in the tobit model remained < 10% even when the censoring % was high.

Simulation Study

What if the data assumptions are not met?

When the underlying data had a lognormal conditional distribution, again the OLS bias was approximately equal to the proportion of censoring while the Tobit parameter bias performed better with bias < 10%.

When the underlying data is normal with increasing variance, the Tobit model performs as poor or more poorly than the OLS model.

Lastly, when the underlying data is lognormal and the variance in increasing with X, the Tobit model again had a greater relative bias than the OLS model.

Example with real CAC data

Example
DCCT/EDIC Data

Study Description

The Diabetes Control and Complications Trial (DCCT) / Epidemiology of Diabetes Interventions and Complications (EDIC) study provides an opportunity to explore the complex relationships among traditional CVD risk factors, glycemia, and CVD outcomes.

As an example, we will examine the relationship between levels of CAC and the waist to hip ratio of each subject adjusted for other known covariates.

Example
DCCT/EDIC Data

Data Analysis

CT was performed on 1205 of the original 1441 subjects (84%) and 1189 have "natural waist to hip ratio" data available.

Data was analyzed by Cleary et al (2006), results were summarized using both logistic regression models (CAC=0, CAC>0) as well as the Tobit censored regression. Their focus was on metabolic memory and the effect of intensive treatment of diabetes on cardiovascular outcomes.

We will only focus on the a more simple age and gender adjusted analysis of the relationship between CAC and WH Ratio.

Example
DCCT/EDIC Data

Results

Of the 1189 subjects with available CAC data, 821 have censored data (69%).

Results from natural WH Ratio (10% Change)	Continuous Models			Categorical Models	
	OLS	OLS (restricted)	Tobit	Binary Logistic	Prop Odds Logistic
	Proc GLM	Proc GLM	Proc QLIM/LIFEREG	Proc Logistic	Proc Logistic
Parameter ± SE	0.391 ± 0.092	0.123 ± 0.152	1.190 ± 0.282	0.447 ± 0.110	0.405 ± 0.103
Statistic	t=4.24	t=0.81	X^2=17.86	X^2=16.43	X^2=15.40
P Value	P<0.001	p=0.421	p<0.001	p<0.001	p<0.001
				1.56 (1.26-1.94)	1.50 (1.23-1.84)

$OLS_\beta = \beta - (OLS_{Bias} * \beta)$ thus 1.19-(1.19*0.69)=0.368 ≈ 0.391. So, 1.19 is not the true underlying Beta, but is probably close.

Conclusions and other work

Conclusions

Some basic conclusions

OLS Regression models will provide heavily biased estimated in the presence of censoring.

The Tobit regression model appears to be more robust in the presence of non normal data than OLS.

OLS performs better than the Tobit model in the presence of Heteroscedasticity.

Most published studies use a Logistic and/or Tobit regression modeling approach.

Conclusions

Tobit model in SAS

```
proc qlim data=cac;
        where (x ne .);
                model cac = x;
                endogenous cac ~ censored (lb=0);
                output out = fitted predicted expected conditional xbeta errstd;
run;

data fitted;
        set fitted;
        cdf = probnorm (xbeta_cac/ errstd_cac);
        pdf = PDF('NORMAL',xbeta_cac/errstd_cac);
                y_censored_expected = cdf * xbeta_cac + errstd_cac * pdf;
                        /* This is E(Y|X)*/
run;
```

The Tobit model can also be implemented in SAS Proc Lifereg, R (VGAM), STATA (tobit), and Mplus

Further Work

Models used in the literature

Tobit Regression, Logistic regression, OLS Regression, Probit Regression, Risk Regression, Median Test, Generalized Additive Models

Other Suggestions

Two Part Models

Logit-linear & Probit-linear, Han and Kronmal, 2006

Probit/Log Skew normal, Chai and Bailey, 2008

implemented using MLE in proc nlmixed

References

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Collaborators

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Further Work

Is the underlying distribution of log(CAC) truly symmetric and normal?

If not, how biased will the estimates become and how will the methods compare?

Fleishman's Power Transformation Method can be used to add varying levels of skew and kurtosis to the distribution and retest the models noting the bias. (Fleishman, 1978)