TOBIT REGRESSION AND CENSORED CYTOKINE DATA

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Well designed clinical studies theoretically produce accurate data from which a reasonable conclusion(s) may be drawn. Data accuracy may be hindered by the measurement tool or device. Additionally, the data may be in such a form that it is problematic from an analytic and interpretive point of view. An example of such a problematic form may be seen in censored, sample-selected, or truncated data.

Clinical data may be particularly prone to censoring or truncation since various assays used to measure patient parameters have limited sensitivity. Lower and upper limits of assay sensitivity may have a direct impact on the clinical diagnosis and prognosis of the patient, especially if the patient is a high risk critical care patient.

The aim of this report is to estimate mean cytokine levels using various approaches, including the arithmetic and geometric mean, and mean estimation from a tobit model. The data set is from the Department of Critical Care Medicine and contains values for several cytokines from 1753 patients (discharge status) or 1610 patients (follow-up status), including Interleukin 6 (IL-6), Interleukin 10 (IL-10), and Tumor Necrosis Factor (TNF). A brief overview of the immune system and its relationship to cytokine production will be presented prior to an explanation of the estimation procedures. Finally, recommendations for estimating a mean from the censored data set will be presented.

Although not specific to Critical Care Medicine, the problem of censored data is evident in many areas of study, specifically Public Health. Guidelines for dealing with censored data would be a significant and valuable tool for Public Health professionals.

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1. INTRODUCTION

Well designed clinical studies theoretically produce accurate data from which a reasonable conclusion(s) may be drawn. However well intentioned investigators may be, the data may fail to accurately characterize the population from which the parameters were measured. Additionally, the data may be in such a form that it is problematic from an analytic and interpretive point of view. An example of such a problematic form may be seen in censored, sample-selected, or truncated data.

The problem of censored, sample-selected, or truncated data is evident in business/economic, social science, and medical literatures.[1] However, it was in the economics literature where the seminal paper by Tobin[2] in 1958 laid the foundation for the contemporary analysis and interpretation of censored, sample-selected, or truncated data. But no matter what problematic form the data may take, the ultimate goal of the analysis is to provide the best estimate of the population parameters.

Clinical data may be particularly prone to censoring or truncation since various assays used to measure patient parameters have limited sensitivity. Lower and upper limits of assay sensitivity may have a direct impact on the clinical diagnosis and prognosis of the patient, especially if the patient is a high risk critical care patient. In this situation it is essential that the clinician have a tool that best estimates the parameter in question to provide the patient with a reliable diagnosis and effective treatment plan that will, in turn, offer the most accurate prognosis.

One major factor in the management of the Critical Care Patient is the assessment of laboratory values. One measurable parameter that may be pertinent in Critical Care patient management is serum Cytokine level. Cytokine levels may be pertinent since cytokine

production is associated with immune response, inflammation, and sepsis, which are significant events for high risk patients. However, cytokine assay sensitivity may hinder the clinician's ability to effectively and efficiently treat their patients when the limited sensitivity results in a cytokine level cutoff value.

The aim of this report is to estimate mean cytokine levels using various approaches, including the arithmetic and geometric mean, and mean estimation from a tobit model. The data set is from the Department of Critical Care Medicine and contains values for several cytokines from 1788 patients, including Interleukin 6 (IL-6), Interleukin 10 (IL-10), and Tumor Necrosis Factor (TNF). A brief overview of the immune system and its relationship to cytokine production will be presented prior to an explanation of the estimation procedures. Finally, recommendations for estimating a mean from the censored data set will be presented.

2. BACKGROUND AND REVIEW

2.1. Immunology

The human immune system acts as a protective mechanism against pathogens which cause disease, and tissue damage. At the core of the immune system is the body's ability to recognize "non-self" molecules. Non-self molecules (antigens) are foreign molecules composed of protein(s) and/or carbohydrate(s) that stimulate an immune response. The immune system is regulated through the innate and adaptive immune responses.

2.1.1. Overview of Immune System

Innate Immunity

The innate immune response functions through physical barriers to entry, mechanical actions, biochemical defenses, and the actions of specialized cells. The epidermis and mucous membranes act as physical barriers against pathogen entry into the host's body, while the mechanical actions of sneezing, coughing and vomiting physically expel the pathogens. Additionally, the cilia that line the respiratory tract also brush pathogens along with a sweeping motion to eliminate them from the body.

The acidic environment of the stomach and the digestive enzymes found in mucus and tears provide biochemical barriers. Additional biochemical defense is possible through complement (anti-bacterial) and interferon (anti-viral). The specialized cells that afford innate defense include phagocytes, Natural Killer (NK), M, and Langerhan's cells found in the blood and

various organ systems. Finally, the inflammatory response attracts leukocytes to the site of an infection.

The inflammatory response is a series of events that results in redness, swelling, and occasionally, pain at the infection site. When common bacterial antigens are present, macrophages are stimulated to produce signaling proteins called cytokines. Examples of cytokine effects include increased production of leukocytes in the bone marrow, increased attraction of leukocytes to the infection site, increased expression of adhesion molecules found in the membranes of epithelial cells that line the blood vessels, and an increase in the amount of fluid that enters the tissue from the circulation. Leukocytes possess receptors to adhesion molecules that place them in a favorable position to enter the surrounding tissue. Excess fluid in the tissue results in increased levels of antibacterial molecules that are naturally occurring in lymph fluid.

Adaptive Immunity

The adaptive immune response functions essentially through antibody production and various actions of T cells. Adaptive immunity, although not permanent, can be very enduring. A characteristic that differentiates adaptive immune response from innate response is that adaptive immunity is antigen-specific and provides an efficient and effective defense against repeat infection(s).

Exposure and heredity play crucial roles in each individual's adaptive immune response. Exposure may be classified as either active or passive. Examples of active immunity are the natural infection with the influenza virus, or vaccination with an attenuated influenza virus. Active immunity requires a couple of weeks after infection to become established, but once

established may last for years. Passive immunity occurs with the direct transfer of antibodies or T cells (cellular immunity). Examples of passive immunity include antibody transfer from mother to child through breast milk, mother to fetus through the placenta, the infusion of animal antibodies into humans as a treatment for poisonous venom, and bone marrow transplantation.

Immunity at the cell and organ level

Immune cells are commonly called white blood cells or leukocytes. Leukocytes play a key role in both the innate and adaptive immune system. Leukocytes of the innate system are phagocytes and are *not* antibody specific. Phagocytes are either macrophages or polymorphonuclear leukocytes. Macrophages and polymorphonuclear leukocytes bind to protein surface molecules that are common on many pathogens, and engulf and kill them. Large granular lymphocytes that offer protection from virus infected cells and cancer cells are the Natural Killer (NK) cells of the innate system. NK cells lyse the infected cell or cancer cell, whereas macrophages engulf them. The NK cells are part of the innate system since they lack antigen specificity. Macrophages are also responsible for cytokine production (see below).

Leukocytes that *are* antigen-specific are part of the adaptive immune system. Leukocytes begin development in the bone marrow, whereas T cells complete their development in the Thymus. During development each cell acquires specific individual antigen receptors and co-receptors, receptors to cytokines, and receptors to adhesion molecules (found on epithelial cell membranes). Antigen-specific lymphocytes multiply when their receptors encounter the antigen. Their progeny, or clones, contain the same antigen specificity as the parent cell that was activated.

The organs of the immune system are classified as either primary or secondary. The primary organs include the bone marrow and the Thymus. The secondary organs are meeting places for antigen and leukocyte. The secondary organs include the spleen and the lymph nodes. Special clusters of epithelia cells (M cells) and lymphocytes also occur where exposure to antigen is most likely. Exposure is most likely at the membranes lining respiratory, digestive, and urogenital systems.

Antibodies

Antibodies, or immunnoglobulins, are Y-shaped proteins that are composed of two identical binding regions at the upper part of the Y, but vary according to antigen specificity, and an invariable region on the lower portion of the Y. The invariable lower portion accounts for the five different isotypes of antibody including, IgA, IgD, IgE, IgG, and IgM. Antibodies are either membrane bound as receptor sites on B cells or unbound molecules that are secreted by B cells after stimulation from cytokines from T cells.

Antigen elimination is the primary function of the antibodies. The binding of antibodies to antigen results in neutralization and opsonization. Neutralization occurs when the antibodies bind to bacterial toxins or extracellular proteins and inactivates them. Opsonization occurs when antibodies (or complement) form a coat surrounding the pathogen which then enables binding to phagocytes and elimination (or lysing).

Isotypes

The IgM and IgD antibodies (immunoglobulins) are membrane bound and function as receptors on B cells. IgM, the first unbound antibody secreted by an activated B cell, is a very efficient

antigen-binder and a complement activator, but is also a very large molecule. Its large size limits its efficiency of infiltration into various tissues.

IgG and IgA are secreted by the B cells after they are activated by cytokines from the T cells. IgG and IgA neutralizes toxins and viruses by blocking the host cells binding capabilities. IgG is predominantly in the serum, thus neutralization and opsonization by IgG prevents the toxins and viruses from entering the host's cells. IgA is present in mucus secretions, including breast milk and those found in the lining of the digestive, respiratory, and urogenital systems.

IgE is the immunoglobulin responsible for histamine release that occurs with allergic reactions by binding to mast cells. IgE also functions as protection again antigens associated with parasites.

2.1.2. Overview of Cytokines

A key component in the immune response is cell-to-cell signaling. Cell-to-cell signaling is achieved through cytokine secretion. Cytokine is a generic term for a family of small proteins with short half lives that regulate and modulate the immune system. They are predominately produced by helper T cells and macrophages and result in activation, inhibition, inflammation, differentiation, proliferation, and cell death. Specific cytokines include lymphokines, monokines, chemokines, and interleukin. Lymphokines and monokines are produced by lymphocytes and monocytes, respectively. Chemokines produce chemotactice activity, i.e. they attract leukocytes to the site of an infection. Interleukins are cytokines produced by one type of leukocyte that causes a response in a different type of leukocyte.

Cytokines are capable of producing a variety of actions, including autocrine, paracrine and endocrine actions. Autocrine, paracrine and endocrine refer to actions upon, the same cells that

secrete the cytokine, cells in close proximity, and distant cells, respectively. Additionally, cytokines exhibit redundancy and pleiotropy. Redundancy refers to different cytokines producing similar functions or effects. Pleiotropy refers to one cytokine activating many different types of target cells, or for many different cytokine-producing cells to produce the same cytokine. Other characteristics of cytokines are their ability to behave in a synergistic or antagonistic fashion, and for the production of one cytokine to initiate production of another cytokine in a different cell.

Cytokines may also be categorized by function. Immune cell proliferation and differentiation characterizes the largest group of cytokines. This group includes TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, interferon gamma (IFNγ), and Granulocyte Monocyte Colony-Stimulating Factor (GM-CSF). Another group is characterized by its ability to inhibit viral replication in infected cells and simultaneously stimulating antigen-presenting MHC expression. This group includes Interferon alpha (IFNα) and Interferon beta (IFNβ). Interleukin-8, MCP-1, MIP-1α, MIP-1β, Lemphotactin, and Fractalkine represent the chemokine group. Finally, there is also a group that is composed of cytokines that inhibit inflammatory cytokine production by macrophages and includes IL-10 and IL-13.

Additional details concerning IL-6, IL-10, and TNF are provided since they are the focus of this analysis and report.

2.1.2.1. TNF

TNF is a superfamily of molecules first recognized when certain cancer patients exhibited regression of tumors following infection. Tumor Necrosis Factor alpha (α) and beta (β) are only two types of the many specific molecules found within this superfamily.

TNFα is a bioactive nonglycosylated transmembrane or soluble polypeptide. The transmembrane form is 233 amino acids long, has a mass of 26 KDa and consists of cytoplasmic, transmembrane, and extracellular regions composed of 29, 28 and 176 amino acids respectively.[3] A soluble homotrimeric molecule of 157 amino acids is formed when a proteolytic TNFα converting enzyme cleaves the membrane bound protein.[4] The soluble, circulating form is reported to be more potent than the membrane bound form and normal levels are 10-80 pg/mL.[5] [6]

Many different cells express TNFα. The various cell types include T helper cells [7] (CD4 and CD8), macrophages, mast cells,[8] osteoblasts,[9] pancreatic cells,[10] fat cells,[11] dendritic cells,[12] neurons,[13] astrocytes,[14] and monocytes.[15] The effect of the TNFα expressed by these cells is cytotoxic to tumor cells and induces other cell types to secrete other cytokines involved with the inflammatory response.

TNFβ is a circulating 25 kDa glycosylated polypeptide; one composed of 171 amino acids, the other of 194 amino acids.[16] TNFβ binds to the same receptors as TNFα and circulating levels are reported to be ~150pg/mL.[17] Unlike TNFα, TNFβ is not a transmembrane protein and only has a circulating or membrane-associated form. NK cell, and T and B cells express TNFβ.[18] While the effects of TNFβ are similar to those of TNFα, TNFβ also increases the phagocytic activity of macrophages and neutrophils.

2.1.2.2. IL-6

IL-6 is a relatively recent name given to a cytokine that was associated with many different functions and having equally many different names. It was only after a common gene was identified that these differently named molecules based on different functions became known collectively as IL-6.[19] This phenomenon is the basis of the pleiotrophic characteristic of this

cytokine. Membership in the IL-6 family is related to its helical structure and receptor characteristics.[20 21]

IL-6 is a secreted glycoprotein with a mass of 22-27 kDa. IL-6 is originally translated into a molecule of 212 amino acids, ending as a mature molecule of 184 amino acids.[22] Normal circulating levels of IL-6 are reported to be ~1 pg/mL.[23] Elevations of IL-6 are also reported in association with menstruation,[24] melanoma,[25] and post-surgery.[26]

As seen with TNF, various cell types express IL-6. Expression of IL-6 is seen in T cells (CD8),[27] fat cells,[28] fibroblasts,[29] osteoblasts,[30] mast cells,[31] astrocytes,[32 33] pigment cells in the retina,[34] cerebral cortex and sympathetic neurons,[35 36] eosinophils,[37] neutrophils,[38] monocytes,[39] epithelial cells of the large intestine,[40] synoviocytes,[41] pancreatic cells,[42] and others.

IL-6 has been associated with various activities. IL-6 is described as both a pro- and anti-inflammatory molecule[43] as well as a co-stimulator (with IL-1) in T cell activation and plasma cell proliferation.[44] IL-6 also increases hematopoiesis[45] and modulates resorption of bone.[46]

2.1.2.3. IL-10

IL-10 is a nonglycosylated molecule that weighs 18 kDa and is composed of 178 amino acids with a mature length of 160 amino acids.[47] Normal circulating levels of IL-10 are reported to be ~0.5 pg/mL.

As seen with TNF and IL-6, various cell types express IL-10. Expression of IL-10 is seen in T cells (CD8),[48] macrophages that have been activated,[49] B cells,[50] melanoma cells,[51] NK cells,[52] eosinophils,[53] dendritic cells,[54] and others. The secretion of IL-10 suppresses cytokine production by the T_H1 subset of T helper cells. IL-10 modulates function in various cell types including neutrophils, monocytes, dendritic cells, and mast cells and NK cells, as well as T and B cells.

IL-10 has an anti-inflammatory effect on neutrophils:

- Blocks IL-1β and TNFα and inhibits secretion of IL-8, MIP-1α, MIP-1 β[55]
- Results in less superoxide being produced, which hinders anti-body dependent cytotoxicity.[56]

IL-10's effect on monocytes:

- Results in decreased IL-8 production[57]
- Results in increased hyaluronectin in connective tissue (which is associated with decreased migration of metastatic tumor cells)[58]
- Reduces MHC-II expression on the cell surface.[59]

IL-10 has an immunosuppressive effect on dendritic cells. IL-10 results in:

- Increases in macrophages (while this may appear beneficial, macrophages are not good antigen presenting cells)[60]
- Dendritic cells being less efficient at stimulating T cells[61]
- Immobile dendritic cells.[62]

In NK cells, IL-10:

- Promotes TNFα and GM-CSF production[63]
- May increase IL-2 induced NK cell proliferation[64]
- Increases NK cells cytotoxicity with the aid of IL-12 and IL-18.[65]

IL-10 has the opposite effect in mast cells compared to NK cells. In mast cells, IL-10 results in:

- Blocked production of TNFα and GM-CSF[66]
- Increased release of histamine.

IL-10 effects T cell function by:

- Suppressing IL-2[67]

- Inhibiting T cell apoptosis[68]
- Induction of CD8 chemotaxis.[69]

IL-10 effects B cell function by:

- Initiating differentiation/growth and promotes plasma cell formation[70]
- Inducing the production of IgA[71]
- Inducting the production of IgG1 and IgG3 (in the absence of TGFβ).[72]

2.2. The Data – Censored, Sample-Selected, Truncated data

Many investigators use ordinary least squares (OLS) regression in the event of a continuous outcome variable. However, deviation from the assumptions of ordinary least squares will result in biased estimates. Uninformed investigators may also perform OLS on limited datasets, or datasets with missing values, while others may sort their data to eliminate groups with missing values and then perform OLS. These types of datasets often have a problem commonly referred to as a censoring problem, but may be categorized as either censored, sample selected, or truncated. To delineate the differences between these types of data see Table 1.[73]

Table 1. Definitions of Censored, Sample-Selected, and Truncated Variables

Data/Sample	Dependent Variable	Independent Variable(s)
Censored	y is known exactly only if some criterion defined in terms of the value of y is met, such as $y > c$ (or $y < c$) . y is a truncated random variable.	x variable values are observed for all of the sample, regardless of whether y is known exactly.
Sample selected	y is observed only if some criterion defined in terms of another random variable, z, is met such as if $z = 1$. y is a truncated random variable.	x and w are observed for all the sample, regardless of whether y is observed or not.
Truncated	y is observed only if some criterion defined in terms of the value of y is met, such as $y > c$ (or $y < c$). y is a truncated random variable.	Independent variables are observed only if y is observed

The dataset in this report is classified as censored from below. A variable is left censored (censored from below) if for some value y, the exact value of y taken is $y > c$. For other values of y it is only know that $y \leq c$. A variable may be right censored (censored from above) if for

some value y, the exact value of y taken is less than some threshold, $y < d$. For other values of y it is only know that $y \geq d$. A final example of censored data is where the data is censored from the left and the right (ie. from below and above). In this instance, $c < y < d$; where the exact values of y are known between the lower and upper limits. However, if outside of the specified range, it is only known that $y \leq c$ and/or $y \geq d$.

2.2.1. The Tobit Model

The simplest method for analysis for censored data is the Tobit model.[74] The Tobit model may be interpreted in terms of an underlying latent variable, y^*, of which y is the realized observation. Another way of saying this, is that y^* is the true value, and y is the value that is observed (remembering that the value is limited or censored). The model may be written in terms of the latent variable y*:

$$y_i^* = x_i^T \beta + u_i$$

where the error term u_i is assumed to be independent and normally distributed with a mean of zero and a constant variance, σ^2.

The observed and latent variables are related by the following relationship:

$$y_i = y_i^* \text{ if } y_i^* > c$$

$$y_i = c \text{ if } y_i^* \leq c$$

where c is the censoring threshold. In this report, the censoring thresholds for tnf, IL6 and IL10, are 3.9, 4.9, and 4.9, respectively. The model written in terms of the observed variable y, using tnf for example is:

$$y_i = x_i^T \beta + u_i \quad \text{if } > 3.9$$

$$y_i = 3.9 \text{ otherwise.}$$

The purpose of regression is to estimate an intercept (α), a regression coefficient (β), and the standard error of the independent error term, σ (assumed normally distributed). In some circumstances (where certain assumptions met- no correlation between u and x, independence of u_is, zero expectation of u_i, and homoscedasticity) ordinary least squares (OLS) provide estimates that are the best linear unbiased estimators (BLUE), i.e. the estimates have the smallest sampling variance (making them the most efficient) of all the linear unbiased estimators. However, in the case of censored data, maximum likelihood estimation is used to estimate α, β, and σ.

2.2.2. Maximum Likelihood

The goal of maximum likelihood is to find the set of parameters that would have generated the observed sample most often, if the parameters are true of the population. Maximum likelihood is applicable in both the discrete and continuous case. Regardless of type of variable, the first step is to formulate the likelihood function. Formulating a likelihood function first starts with the joint probability distribution

$$f(y_1,y_2,\ldots y_N).$$

And since the sample observations are assumed to be independent, the joint probability is equal to the product of the marginal probabilities

$$f(y_1,f(y_2)\ldots f(y_N).$$

$$= \prod_{1}^{N} f(y_i).$$

Although this equation is identical to the joint probability distribution of the sample, it is something completely different in terms of maximum likelihood estimation. In the case of a joint probability distribution, the parameters of the distribution are fixed, and the y values are variable. In the case of likelihood, the y values are fixed and the parameters are allowed to vary.

For simplifying calculations, the natural logarithm of the likelihood function is then taken, and maximized with respect to each parameter.

The dependent variables in this report (tnf, IL6, and IL10) are continuous, and therefore the probability density function is used to formulate the likelihood function (as opposed to probability mass function). Assuming the population yi's are normally distributed the density function is

$$f(y_i) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp \frac{-[(y_i - \mu)/\sigma]^2}{2} .$$

Taking the product of the densities of the y_i's and then taking the natural logarithm of this function results in the log-likelihood function

$$\sum_{1}^{N} \log\left(\frac{1}{\sqrt{2\pi\sigma^2}}\right) - \frac{1}{2\sigma}(y_i - \mu)^2 .$$

Let $\mu_i = \alpha + \beta x_i$, and substitute into the equation above. This substitution is made since μ varies over the sample resulting in

$$\sum_{1}^{N} \log\left(\frac{1}{\sqrt{2\pi\sigma^2}}\right) - \frac{1}{2\sigma^2}\left(y_i - \left(\alpha + x_i^T \beta\right)\right)^2 .$$

Parameter estimates of α, β, and σ are derived by maximizing the above equation.[75] This is the log-likelihood for the normal error regression model. However, in the tobit model, censored and uncensored observations make separate contributions to the log-likelihood function.

2.2.3. Tobit Model and Maximum Likelihood

Let y_i be the serum cytokine level (tnf, IL6, IL10) of the i^{th} patient in the population of study patients, and let x_i be the value of dead or alive status at discharge or follow-up. The goal is to estimate the vector β, which is the set of population regression parameters relating x_i to the level

of circulating cytokine. The sample is composed of *N* patients, of which N_0 have truncated cytokine (censored) values, and N_1 *(=N-*N_0*)* with observed (uncensored) values.

To formulate the likelihood function for the tobit model it is assumed that

- u_i has a normal distribution,
- the error terms of each observation are independent of each other,
- the error term is independent of the independent variable(s) in the model.[76]

We also have cytokine values for all patients (day 1), and that for uncensored (N_1) observations, the exact value is known.

Contributions to the likelihood come from censored and uncensored observations. The likelihood contains the product of N_0 observations that are censored and N_1 observations that are uncensored. The product of the N_0 observations is

$$\prod_{i=1}^{n_o}(1-\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right))$$

where Φ (unless stated otherwise) denotes the standard normal distribution function *(mean = 0, variance = 1)*.

The product of the N_1 observations is

$$\prod_{i=n_o+1}^{N}\left(\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)\right).$$

However, for the N_1 observations, the exact cytokine values are known, therefore the following term becomes part of the likelihood,

$$\prod_1\frac{1}{\sigma}\frac{\Phi\left[\left(y_i-(\alpha+x_i^T\beta)\right)/\sigma\right]}{\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)}.$$

When the three product terms are multiplied, the $\Phi_i(\cdot)$ term (in the second and third product-terms) cancels.

$$\prod_0\left(1-\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)\right)\prod_1\left(\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)\right)\prod_1\frac{1}{\sigma}\frac{\Phi\left[\left(y_i-x_i^{T'}\beta\right)/\sigma\right]}{\Phi_i}$$

The result is the likelihood function:

$$\prod_0\left(1-\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)\right)\prod_1\Phi\left[\left(y_i-(\alpha+x_i^T\beta)\right)/\sigma\right].$$

The natural logarithm of the likelihood function is:

$$\sum_0\log\left(1-\Phi_i\left(\frac{y_i-\left(\alpha+x_i^T\beta\right)}{\sigma}\right)\right)+\sum_1\log\frac{1}{\sqrt{2\pi\sigma^2}}-\sum_1\frac{1}{2\sigma^2}\left(y_i-x_i^T\beta\right)^2 \quad .$$

Notice that the circled portion (uncensored contribution) of the tobit log-likelihood function is same as the log-likelihood for the normal error regression model in the previous section (1.2.2).

2.2.4. The Delta Method for Standard Error Determination

The *predictnl* command is implemented as an ado-file following an estimation command (e.g. *tobit*) in STATA. The quantities generated by *predictnl* are not scalars, but functions of the data, and are therefore vectors over the observations within the data.

For general prediction,

$$g(\theta,x_i) \qquad \text{for } i = 1,\ldots,n$$

where θ are model parameters and x_i are data for the i^{th} observation (and are assumed to be fixed). In STATA, $g(\theta,x_i)$ is estimated by

$$g(\hat{\theta},x_i)$$

where $\hat{\theta}$ are estimated model parameters stored as e(b) following the estimation command. In STATA, *predictnl* generates the estimated prediction, $g(\hat{\theta}, x_i)$, but also generates the standard error of $g(\hat{\theta}, x_i)$, using the "delta method".[77]

The delta method expands a function of a random variable about its mean with a one-step Taylor approximation, and then takes the variance.[78] When using predictnl, the transformation $g(\theta, x_i)$, is estimated by $g(\hat{\theta}, x_i)$, for 1x *k* parameter vector θ and the data x_i (which is assumed fixed). The variance of $g(\hat{\theta}, x_i)$ is estimated by

$$\hat{Var}\left\{g\left(\hat{\theta}, x_i\right)\right\} = GVG'$$

where G is the vector of derivatives

$$G = \left\{ \frac{\partial g(\theta, x_i)}{\partial \theta} |_{\theta=\hat{\theta}} \right\}_{(1xk)}$$

and V is the estimated variance-covariance matrix of $\hat{\theta}$.[79]

For the instance presented here the mean is estimated by $\exp(x^T \hat{\beta})$. Using the delta method, the estimated variance is given by:

$$\left(e^{x\hat{\beta}}, \quad xe^{x\hat{\beta}}\right) \begin{pmatrix} V(\hat{\beta}_0) & C\left(\hat{\beta}_0, \hat{\beta}_1\right) \\ C\left(\hat{\beta}_0, \hat{\beta}_1\right) & V\left(\hat{\beta}_1\right) \end{pmatrix} \begin{pmatrix} e^{x\hat{\beta}} \\ xe^{x\hat{\beta}} \end{pmatrix}$$

$$= \left(V(\hat{\beta}_0)e^{x\hat{\beta}} + C\left(\hat{\beta}_0, \hat{\beta}_1\right)xe^{x\hat{\beta}}, \quad C\left(\hat{\beta}_0, \hat{\beta}_1\right)e^{x\hat{\beta}} + V(\hat{\beta}_1)xe^{x\hat{\beta}}\right) \begin{pmatrix} e^{x\hat{\beta}} \\ xe^{x\hat{\beta}} \end{pmatrix}$$

$$= \left(V(\hat{\beta}_0)\left(e^{x\hat{\beta}}\right)^2 + C\left(\hat{\beta}_0, \hat{\beta}_1\right)x\left(e^{x\hat{\beta}}\right)^2 + \quad C\left(\hat{\beta}_0, \hat{\beta}_1\right)x\left(e^{x\hat{\beta}}\right)^2 + V(\hat{\beta}_1)x^2\left(e^{x\hat{\beta}}\right)^2\right)$$

$$= \quad \left(e^{x\hat{\beta}}\right)^2\left(V(\hat{\beta}_0) + 2C\left(\hat{\beta}_0, \hat{\beta}_1\right)x + \quad V(\hat{\beta}_1)x^2\right).$$

2.3. Additional Analysis

In addition to tobit estimates of mean cytokine levels in the study population, the arithmetic and geometric mean are also provided.

2.3.1. Arithmetic Mean

The arithmetic mean of a set of numbers is the sum of all the members of the set divided by the number of items in the set. If the data set is denoted by $X = \{x_1, x_2, ..., x_n\}$. The arithmetic mean is calculated as:

$$\bar{x} = (x_1 + x_2 + ... + x_n)/n$$

or alternatively

$$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$

The arithmetic mean is greatly influenced by outliers.[80]

2.3.2. Geometric Mean

The geometric mean is to multiplication as the arithmetic mean is to addition. Just as adding *n* terms all equal to the arithmetic mean yields the sum $x_1 + ... + x_n$, so multiplying *n* factors all equal to the geometric mean yields the product $x_1 ... x_n$ (these n numbers must be non-negative). The geometric mean is

$$(x_1 x_2 ... x_n)^{1/n}$$

or

$$\sqrt[n]{x_1 x_2 ... x_n}\ .$$

The geometric mean is less affected by extreme values than the arithmetic mean and is useful for some positively skewed distributions.[81]

3. RESULT

The data set consists of serum cytokine levels measured on day 1 for 1753 critical care patients. Tumor necrosis factor , Interleukin-6, and Interleukin-10 are coded as tnf, il6, and il10 respectively. Tobit estimates of mean cytokine levels are for dead or alive status at discharge and follow up. Dead and alive are coded as 0 and 1 respectively. Discharge and follow up are coded as "dc" and "fu", respectively. Cytokine values were available for 1753 patients at discharge. However, 143 patients were lost to follow up.

Laboratory values for tnf, il6 and il10 are left censored. The lower limit for tnf, il6 and il10 are 4, 4, and 5 respectively. The number of left censored cytokine values for tnf, il6, and il10 *at discharge*, were 670 (38.22%), 248 (14.15%), and 854 (48.72%), respectively. The number of left censored cytokine values for tnf, il6, and il10 *at follow up*, were 610 (38.89%), 230 (14.29%), and 788 (48.94%), respectively.

Microsoft Excel, Microsoft Access, and STATA 8.0 SE were used for all data analyses. A summary table for mean estimates of tnf, IL6 and IL10 for discharge status and follow-up status are presented below. The STATA output may be found in Appendix A.

Table 2. Frequency of censored cytokine values and dead/alive status at discharge and follow-up

	Discharge Status (N=1753)		Followup Status (N=1610)	
	Frequency	**Percent**	**Frequency**	**Percent**
tnf	670	38.22	610	38.89
IL6	248	14.15	230	14.29
IL10	854	48.72	788	48.94
dead	78	4.45	231	14.35
alive	1675	95.55	1379	85.65

N=1610 at follow up due to dead/alive status missing for 143 patients.

Table 3. Comparison of mean estimates for TNF, IL6, and IL10 for death at discharge based on the tobit model, the arithmetic and the geometric mean. Note that the population is the 1753 individuals with both complete lab and follow up data with 78 reported deaths at discharge and 1675 subjects alive at hospital discharge. Standard errors are given in parentheses below the mean.

Cytokine	Estimated tobit mean for dead at discharge	Estimated arithmetic mean for dead at discharge	Estimated geometric mean for dead at discharge	Estimated tobit mean for alive at discharge	Estimated arithmetic mean for alive at discharge	Estimated geometric mean for alive at discharge
TNF	8.2286 (1.0021)	17.6256 (3.9608)	9.70	5.1884 (0.1472)	10.4444 (0.7426)	6.90
IL6	167.1379 (38.3026)	2895.464 (1648.548)	172.46	37.0714 (1.8622)	329.1224 (33.4703)	43.28
IL10	11.3489 (2.2705)	47.11282 (13.2713)	15.64	4.9238 (0.2483)	22.34845 (1.6798)	9.61

Table 4. Comparison of mean estimates for TNF, IL6, and IL10 for death at follow-up based on the tobit model, the arithmetic and the geometric mean. Note that the population is the 1753 individuals with both complete lab and follow-up data with 231 reported deaths at follow-up and 1379 subjects alive at follow up and 143 with missing values. Standard errors are given in parentheses below the mean.

Cytokine	Estimated tobit mean for dead at follow-up	Estimated arithmetic mean for dead at follow-up	Estimated geometric mean for dead at follow-up	Estimated tobit mean for alive at follow-up	Estimated arithmetic mean for alive at follow-up	Estimated geometric mean for alive at follow-up
TNF	7.1808 (0.5058)	13.7311 (1.5252)	8.65	5.0828 (.01565)	10.0451 (0.7933)	6.77
IL6	77.9086 (10.4984)	1302.035 (575.8675)	83.81	35.2435 (1.9688)	318.4954 (33.0279)	41.62
IL10	7.7613 (0.9265)	30.8952 (5.1314)	12.17	4.7229 (.2623)	21.8598 (1.8900)	9.44

4. CONCLUSION / RECOMMENDATION

Three different methods were presented to estimate the mean cytokine levels of 1753 critical care patients. An accurate estimate of serum levels of TNF, IL6 and IL10 is important since elevated cytokine levels have been associated with tissue damage and a heightened immune response. However, when quantifying assays have a limited range of sensitivity, a large portion of the serum samples tested may fall below or above the accurate range of the assay. The tobit regression provides a method for estimation when dealing with censored data. The arithmetic and geometric means are presented for comparison.

I would not recommend using the arithmetic mean to estimate cytokine levels with this dataset since the data is highly skewed. The arithmetic mean does not take censored laboratory values into account and has a larger standard error associated with its mean when compared to the tobit estimate.

Although the geometric mean is less affected by extreme values than the arithmetic mean and is useful for some positively skewed distributions,[82] I also would not recommend using the geometric mean for estimating the mean cytokine levels with this cytokine dataset. The geometric mean is similar to the arithmetic mean in that it does not account for the censored values.

Of the three estimation methods presented, I would recommend using the tobit model for estimation purposes. I would also recommend that the data be log transformed before the analysis and that the delta method be used to estimate the standard error. Although the tobit model accounts for censored values, it is assumed that the underlying latent variable of the model:

$$y_i^* = \quad x_i^T \beta \quad + u_i,$$

is the correct functional form for the relationship between the latent cytokine level, and discharge or follow-up status. However, other relevant variables may have been omitted from the specification[83] and further research may conclude that a more complex model, than the one presented here, may reveal a more clinically meaningful estimate.

5. APPENDIX A: STATA Output

```
-------------------------------------------------------------------------------
---------------
       log:  C:\Documents and Settings\RSITLO\Desktop\TOD\Tobit_LWDeltaSE.log
  log type:  text
 opened on:  24 Feb 2005, 14:13:51

. do "C:\DOCUME~1\RSITLO\LOCALS~1\Temp\STD030000.tmp"

. * estimating mean tnf and the std error of the predicted value - from STATA manual
for "predictnl"
> pg 225)
.
. **Make sure to check that path for data file is correct before running on different
computers
.
. **** FOR TNF
. **** FOR TNF
. **** FOR TNF
.
.
. * FOR TNF DISCHARGE STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lntnf dc, ll

Tobit estimates                                   Number of obs   =       1753
                                                  LR chi2(1)      =      13.56
                                                  Prob > chi2     =     0.0002
Log likelihood = -2120.2731                       Pseudo R2       =     0.0032

------------------------------------------------------------------------------
       lntnf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          dc |  -.4612006   .1246857    -3.70   0.000    -.7057491   -.2166521
       _cons |   2.107614   .1217833    17.31   0.000     1.868758    2.34647
-------------+----------------------------------------------------------------
         _se |   1.039942   .0242969           (Ancillary parameter)
------------------------------------------------------------------------------

  Obs. summary:        670  left-censored observations at lntnf<=1.360977
                      1083     uncensored observations

. predict lntnfdcxb, xb

. sort dc

. by dc: summarize lntnfdcxb
```

```
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lntnfdcxb |        78    2.107614           0   2.107614   2.107614

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lntnfdcxb |      1675    1.646413           0   1.646413   1.646413


. generate esttnfdcxb=exp(lntnfdcxb)

. sort dc


. by dc: summarize esttnfdcxb

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  esttnfdcxb |        78    8.228582           0   8.228582   8.228582

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  esttnfdcxb |      1675    5.188336           0   5.188336   5.188336


.
.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)

. sort dc

. by dc: summarize pxb_se

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |        78    .1217833           0   .1217833   .1217833

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |      1675    .0283636           0   .0283636   .0283636


. generate se=pxb_se*(exp(pxb))

. sort dc
```

```
. by dc: summarize se

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |        78    1.002104           0   1.002104   1.002104

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1675    .1471599           0   .1471599   .1471599


.
.
.
. ** FOR TNF FOLLOWUP STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lntnf fu, ll

Tobit estimates                                   Number of obs   =       1610
                                                  LR chi2(1)      =      20.41
                                                  Prob > chi2     =     0.0000
Log likelihood = -1939.0459                       Pseudo R2       =     0.0052

------------------------------------------------------------------------------
       lntnf |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          fu |   -.345545   .0761716    -4.54   0.000    -.4949509   -.1961391
       _cons |   1.971414   .0704406    27.99   0.000     1.833249    2.109579
-------------+----------------------------------------------------------------
         _se |   1.026036   .0249322           (Ancillary parameter)
------------------------------------------------------------------------------

  Obs. summary:        610  left-censored observations at lntnf<=1.360977
                      1000     uncensored observations

. predict lntnffuxb, xb
(143 missing values generated)

. sort fu

. by fu: summarize lntnffuxb

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lntnffuxb |       231    1.971414           0   1.971414   1.971414

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
```

```
-------------+---------------------------------------------------------
   lntnffuxb |      1379    1.625869           0   1.625869   1.625869

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
   lntnffuxb |         0


. generate esttnffuxb=exp(lntnffuxb)
(143 missing values generated)

. sort fu

. by fu: summarize esttnffuxb

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
  esttnffuxb |       231    7.180821           0   7.180821   7.180821

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
  esttnffuxb |      1379    5.082833           0   5.082833   5.082833

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
  esttnffuxb |         0


.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)
(143 missing values generated)

. sort fu

. by fu: summarize pxb_se

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
      pxb_se |       231    .0704406           0   .0704406   .0704406

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+---------------------------------------------------------
      pxb_se |      1379     .030785           0    .030785    .030785
```

```
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |         0


. generate se=pxb_se*(exp(pxb))
(143 missing values generated)

. sort fu

. by fu: summarize se

-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |       231    .5058214           0   .5058214   .5058214

-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1379    .1564751           0   .1564751   .1564751

-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |         0


.
.
. ***** IL6
. ***** IL6
. ***** IL6
.
. * FOR IL6 DISCHARGE STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lnil6 dc, ll

Tobit estimates                                   Number of obs   =       1753
                                                  LR chi2(1)      =      40.72
                                                  Prob > chi2     =     0.0000
Log likelihood = -3461.2358                       Pseudo R2       =     0.0058

------------------------------------------------------------------------------
       lnil6 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          dc |  -1.505972   .2345922    -6.42   0.000    -1.966083   -1.045862
       _cons |   5.118819   .2291676    22.34   0.000     4.669348     5.56829
-------------+----------------------------------------------------------------
         _se |   2.018852    .038088           (Ancillary parameter)
------------------------------------------------------------------------------
```

```
  Obs. summary:        248  left-censored observations at lnil6<=1.589235
                      1505     uncensored observations

. predict lnil6dcxb, xb

. sort dc

. by dc: summarize lnil6dcxb

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lnil6dcxb |        78    5.118819           0   5.118819   5.118819

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lnil6dcxb |      1675    3.612847           0   3.612847   3.612847


. generate estil6dcxb=exp(lnil6dcxb)

. sort dc

. by dc: summarize estil6dcxb

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  estil6dcxb |        78    167.1379           0   167.1379   167.1379

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  estil6dcxb |      1675    37.07143           0   37.07143   37.07143


.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)

. sort dc

. by dc: summarize pxb_se

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |        78    .2291676           0   .2291676   .2291676
```

```
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |      1675    .0502337           0   .0502337   .0502337


. generate se=pxb_se*(exp(pxb))

. sort dc

. by dc: summarize se

-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |        78    38.30259           0   38.30259   38.30259

-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1675    1.862235           0   1.862235   1.862235


.
.
. ** FOR IL6 FOLLOWUP STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lnil6 fu, ll

Tobit estimates                                   Number of obs   =       1610
                                                  LR chi2(1)      =      29.35
                                                  Prob > chi2     =     0.0000
Log likelihood = -3186.5002                       Pseudo R2       =     0.0046

------------------------------------------------------------------------------
       lnil6 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          fu |  -.7932545   .1458047    -5.44   0.000    -1.079242   -.5072673
       _cons |   4.355537   .1347528    32.32   0.000     4.091227    4.619846
-------------+----------------------------------------------------------------
         _se |   2.034854   .0400979           (Ancillary parameter)
------------------------------------------------------------------------------

  Obs. summary:        230  left-censored observations at lnil6<=1.589235
                      1380     uncensored observations

. predict lnil6fuxb, xb
(143 missing values generated)

. sort fu

. by fu: summarize lnil6fuxb
```

```
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lnil6fuxb |       231    4.355536           0   4.355536   4.355536

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lnil6fuxb |      1379    3.562282           0   3.562282   3.562282

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
   lnil6fuxb |         0


. generate estil6fuxb=exp(lnil6fuxb)
(143 missing values generated)

. sort fu

. by fu: summarize estil6fuxb

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  estil6fuxb |       231    77.90861           0   77.90861   77.90861

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  estil6fuxb |      1379    35.24353           0   35.24353   35.24353

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  estil6fuxb |         0


.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)
(143 missing values generated)

. sort fu

. by fu: summarize pxb_se

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
```

```
-------------+--------------------------------------------------------
      pxb_se |       231    .1347528           0   .1347528   .1347528

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |      1379    .0558627           0   .0558627   .0558627

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |         0


. generate se=pxb_se*(exp(pxb))
(143 missing values generated)

. sort fu


. by fu: summarize se

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |       231     10.4984           0    10.4984    10.4984

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1379    1.968799           0   1.968799   1.968799

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |         0


.
.
. ***** IL10
. ***** IL10
. ***** IL10
.
. * FOR IL10 DISCHARGE STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lnil10 dc, ll

Tobit estimates                                   Number of obs   =       1753
```

```
                                                LR chi2(1)      =      16.41
                                                Prob > chi2     =     0.0001
Log likelihood = -2346.2507                     Pseudo R2       =     0.0035

------------------------------------------------------------------------------
      lnil10 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          dc |  -.8350396   .2051793    -4.07   0.000    -1.237462   -.4326176
       _cons |   2.429117   .2000641    12.14   0.000     2.036728    2.821507
-------------+----------------------------------------------------------------
         _se |   1.692803   .0442609           (Ancillary parameter)
------------------------------------------------------------------------------

  Obs. summary:        854  left-censored observations at lnil10<=1.589235
                       899     uncensored observations

. predict lnil10dcxb, xb

. sort dc

. by dc: summarize lnil10dcxb

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  lnil10dcxb |        78    2.429117           0   2.429117   2.429117

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  lnil10dcxb |      1675    1.594078           0   1.594078   1.594078


. generate estil10dcxb=exp(lnil10dcxb)

. sort dc

. by dc: summarize estil10dcxb

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 estil10dcxb |        78    11.34886           0   11.34886   11.34886

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 estil10dcxb |      1675    4.923785           0   4.923785   4.923785


.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)

. sort dc
```

```
. by dc: summarize pxb_se

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |        78    .2000641           0   .2000641   .2000641

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |      1675    .0504257           0   .0504257   .0504257


. generate se=pxb_se*(exp(pxb))

. sort dc

. by dc: summarize se

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |        78    2.270499           0   2.270499   2.270499

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1675    .2482854           0   .2482854   .2482854


.
.
. ** FOR IL10 FOLLOWUP STATUS
. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta"

. tobit lnil10 fu, ll

Tobit estimates                                   Number of obs   =       1610
                                                  LR chi2(1)      =      14.78
                                                  Prob > chi2     =     0.0001
Log likelihood =  -2147.814                       Pseudo R2       =     0.0034

------------------------------------------------------------------------------
      lnil10 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          fu |  -.4967164   .1289058    -3.85   0.000    -.7495573   -.2438755
       _cons |   2.049144   .1193811    17.16   0.000     1.814985    2.283302
-------------+----------------------------------------------------------------
         _se |   1.691228    .046283           (Ancillary parameter)
------------------------------------------------------------------------------

  Obs. summary:        788  left-censored observations at lnil10<=1.589235
```

```
                      822     uncensored observations

. predict lnil10fuxb, xb
(143 missing values generated)

. sort fu

. by fu: summarize lnil10fuxb

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  lnil10fuxb |       231    2.049144           0   2.049144   2.049144

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  lnil10fuxb |      1379    1.552427           0   1.552427   1.552427

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
  lnil10fuxb |         0


. generate estil10fuxb=exp(lnil10fuxb)
(143 missing values generated)

. sort fu

. by fu: summarize estil10fuxb

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 estil10fuxb |       231    7.761253           0   7.761253   7.761253

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 estil10fuxb |      1379     4.72292           0    4.72292    4.72292

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 estil10fuxb |         0


.
. **Calculation of standard error is based on Lisa DELTA Method when using predictnl
. predictnl pxb=(xb()), se(pxb_se)
```

```
(143 missing values generated)

. sort fu

. by fu: summarize pxb_se

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |       231    .1193811           0   .1193811   .1193811

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |      1379    .0555424           0   .0555424   .0555424

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
      pxb_se |         0


. generate se=pxb_se*(exp(pxb))
(143 missing values generated)

. sort fu

. by fu: summarize se

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |       231    .9265467           0   .9265467   .9265467

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |      1379    .2623224           0   .2623224   .2623224

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          se |         0


.
.
end of do-file

. log close
       log:  C:\Documents and Settings\RSITLO\Desktop\TOD\Tobit_LWDeltaSE.log
```

```
  log type:  text
 closed on:  24 Feb 2005, 14:14:07
```

STATA output

```
STATA 8.0  from dataset         fulllabvaluesday1_recodecutoffs.dta

tabulate tnf

        tnf |      Freq.     Percent        Cum.
------------+-----------------------------------
        3.9 |        670       38.22       38.22
          4 |         13        0.74       38.96
        4.1 |         17        0.97       39.93
        4.2 |         13        0.74       40.67
------------+-----------------------------------
      Total |      1,753      100.00


. tabulate il6

        il6 |      Freq.     Percent        Cum.
------------+-----------------------------------
        4.9 |        248       14.15       14.15
          5 |          3        0.17       14.32
        5.1 |          5        0.29       14.60
------------+-----------------------------------
      Total |      1,753      100.00


tabulate il10

       il10 |      Freq.     Percent        Cum.
------------+-----------------------------------
        4.9 |        854       48.72       48.72
          5 |          5        0.29       49.00
        5.1 |          6        0.34       49.34
        5.2 |         12        0.68       50.03
------------+-----------------------------------
      Total |      1,753      100.00
```

FOR **dc** and **fu**, **dead = 0, alive=1**

```
tabulate dc

         dc |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |         78        4.45        4.45
          1 |      1,675       95.55      100.00
------------+-----------------------------------
      Total |      1,753      100.00

. tabw dc
Variable|    0     1     2     3     4     5     6     7     8     9 ****     .
--------+-------------------------------------------------------------------------
dc      |   78  1675     0     0     0     0     0     0     0     0    0     0
```

```
. tabulate fu

         fu |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        231       14.35       14.35
          1 |      1,379       85.65      100.00
------------+-----------------------------------
      Total |      1,610      100.00


. tabw fu
Variable|    0     1     2     3     4     5     6     7     8     9 ****     .
--------+-------------------------------------------------------------------------
fu      |  231  1379     0     0     0     0     0     0     0     0    0   143
```

FOR **dc** and **fu**, **dead = 0, alive=1**

```
bysort dc: means tnf il6 il10

--------------------------------------------------------------------------------
-> dc = 0

    Variable |    Type        Obs        Mean       [95% Conf. Interval]
-------------+------------------------------------------------------------
         tnf | Arithmetic      78    17.62564         9.73869   25.51259
             |  Geometric      78    9.696395        7.872858   11.94231
             |   Harmonic      78    7.121124        6.224914   8.318795
-------------+------------------------------------------------------------
         il6 | Arithmetic      78    2895.464       -387.2139   6178.142
             |  Geometric      78    172.4636        106.6768   278.8207
             |   Harmonic      78    39.36164        28.12402   65.55615
-------------+------------------------------------------------------------
        il10 | Arithmetic      78    47.11282        20.68629   73.53935
             |  Geometric      78    15.63691         11.6946   20.90821
             |   Harmonic      78    9.235005        7.924356   11.06512
--------------------------------------------------------------------------------

--------------------------------------------------------------------------------
-> dc = 1

    Variable |    Type        Obs        Mean       [95% Conf. Interval]
-------------+------------------------------------------------------------
         tnf | Arithmetic    1675    10.44436         8.98779   11.90093
             |  Geometric    1675    6.895529        6.667764   7.131074
             |   Harmonic    1675    5.766919        5.639237   5.900517
-------------+------------------------------------------------------------
         il6 | Arithmetic    1675    329.1224        263.4744   394.7704
             |  Geometric    1675    43.28377        39.77457   47.10257
             |   Harmonic    1675    15.82778        15.00716   16.74334
-------------+------------------------------------------------------------
        il10 | Arithmetic    1675    22.34848        19.05381   25.64314
             |  Geometric    1675    9.614716        9.166154   10.08523
             |   Harmonic    1675    7.093285         6.91908    7.27649
--------------------------------------------------------------------------------

.


bysort fu: means tnf il6 il10

--------------------------------------------------------------------------------
-> fu = 0
```

```
    Variable |    Type        Obs        Mean       [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf | Arithmetic     231    13.73117        10.72595   16.73638
             |  Geometric     231    8.650008        7.769028   9.630889
             |   Harmonic     231    6.684285        6.213401   7.232394
-------------+-------------------------------------------------------------
         il6 | Arithmetic     231    1302.035        167.3855   2436.685
             |  Geometric     231    83.81066        65.03224   108.0115
             |   Harmonic     231     24.4099        20.58427   29.98213
-------------+-------------------------------------------------------------
        il10 | Arithmetic     231    30.89524        20.78477    41.0057
             |  Geometric     231    12.17408        10.52017   14.08801
             |   Harmonic     231    8.156444        7.542953   8.878564
-------------------------------------------------------------------------------

-> fu = 1

    Variable |    Type        Obs        Mean       [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf | Arithmetic    1379    10.04511        8.488952   11.60126
             |  Geometric    1379    6.770655        6.530785   7.019334
             |   Harmonic    1379    5.709249        5.572955   5.852377
-------------+-------------------------------------------------------------
         il6 | Arithmetic    1379    318.4954        253.7051   383.2858
             |  Geometric    1379    41.61529        37.90955   45.68327
             |   Harmonic    1379    15.32583        14.46826   16.29146
-------------+-------------------------------------------------------------
        il10 | Arithmetic    1379    21.85975        18.15209   25.56742
             |  Geometric    1379    9.442556        8.963611   9.947093
             |   Harmonic    1379    7.019783        6.832954   7.217117
-------------------------------------------------------------------------------
--more--


sort dc

. by dc: summarize tnf il6 il10

-------------------------------------------------------------------------------
-> dc = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         tnf |        78    17.62564     34.9808         3.9        269
         il6 |        78    2895.464    14559.58         4.9     126000
        il10 |        78    47.11282    117.2089         4.9        896

-------------------------------------------------------------------------------
-> dc = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         tnf |      1675    10.44436    30.39318         3.9        944
         il6 |      1675    329.1224     1369.83         4.9      30215
        il10 |      1675    22.34848    68.74748         4.9       1519


. bysort dc: centile tnf il6 il10, centile(25 50 75)

-------------------------------------------------------------------------------
-> dc = 0

                                                    -- Binom. Interp. --
    Variable |     Obs  Percentile      Centile        [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf |      78         25           3.9             3.9    5.374954
             |                 50          8.05        5.784426    11.21557
             |                 75        18.125        12.60056    24.88224
         il6 |      78         25         41.15        17.24517    67.69851
             |                 50           133        72.16392    225.8034
```

```
             |                 75          482        285.2542    1575.786
        il10 |       78        25          4.9             4.9         5.9
             |                 50          9.3             6.4     18.8451
             |                 75         31.5        23.67533    64.73052
```

```
-> dc = 1

                                                        -- Binom. Interp. --
    Variable |      Obs  Percentile      Centile        [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf |     1675         25           3.9             3.9         3.9
             |                  50           5.4             5.1         5.7
             |                  75          10.2             9.4    10.72504
         il6 |     1675         25           9.7             8.8        11.2
             |                  50          35.5            31.2    39.71063
             |                  75           121             105         134
        il10 |     1675         25           4.9             4.9         4.9
             |                  50           5.1             4.9    5.510629
             |                  75          14.8        13.57768    16.52504
```

```
bysort fu: centile tnf il6 il10, centile(25 50 75)
```

```
-> fu = 0

                                                        -- Binom. Interp. --
    Variable |      Obs  Percentile      Centile        [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf |      231         25           3.9             3.9           4
             |                  50           7.2             6.2         8.8
             |                  75          15.4        11.77895    17.32885
         il6 |      231         25          19.9            16.6    27.60132
             |                  50          67.6        55.84014      93.561
             |                  75           235        177.5987    350.0321
        il10 |      231         25           4.9             4.9         4.9
             |                  50           7.4             6.4     9.53532
             |                  75            23        17.93947    30.52949
```

```
-> fu = 1

                                                        -- Binom. Interp. --
    Variable |      Obs  Percentile      Centile        [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf |     1379         25           3.9             3.9         3.9
             |                  50           5.3               5         5.6
             |                  75           9.7             9.1    10.50225
         il6 |     1379         25           9.1             8.2        10.5
             |                  50          34.1            29.7        39.4
             |                  75           115             101         132
        il10 |     1379         25           4.9             4.9         4.9
             |                  50           4.9             4.9         5.4
             |                  75          14.3        12.50047          16
```

```
-> fu = .

                                                        -- Binom. Interp. --
    Variable |      Obs  Percentile      Centile        [95% Conf. Interval]
-------------+-------------------------------------------------------------
         tnf |      143         25           3.9             3.9         3.9
             |                  50             5        3.953444    6.073278
             |                  75          10.2             7.7    12.96807
         il6 |      143         25          12.1        8.431926    17.66181
             |                  50          32.5        25.63361     52.6854
             |                  75           132        97.61475    202.3615
        il10 |      143         25           4.9             4.9         4.9
             |                  50           5.3             4.9    7.373278
             |                  75          16.3        9.903646    24.91029
```

```
. bysort fu: summarize tnf il6 il10

-------------------------------------------------------------------------------
-> fu = 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         tnf |       231    13.73117    23.18153         3.9        269
         il6 |       231    1302.035    8752.428         4.9     126000
        il10 |       231    30.89524     77.9898         4.9        896

-------------------------------------------------------------------------------
-> fu = 1

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         tnf |      1379    10.04511    29.45811         3.9        944
         il6 |      1379    318.4954    1226.487         4.9      14231
        il10 |      1379    21.85975    70.18643         4.9       1519

-------------------------------------------------------------------------------
-> fu = .

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
         tnf |       143     12.9021    47.59097         3.9        565
         il6 |       143    259.7958    681.2462         4.9       4230
        il10 |       143    26.76294    75.53486         4.9        769


.
clear


.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta", clear


.

. bysort dc: ci tnf il6 il10


-------------------------------------------------------------------------------

-> dc = 0


    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]

-------------+------------------------------------------------------------

         tnf |         78    17.62564    3.960795         9.73869    25.51259

         il6 |         78    2895.464    1648.548       -387.2139    6178.142

        il10 |         78    47.11282     13.2713        20.68629    73.53935


-------------------------------------------------------------------------------

-> dc = 1
```

```
    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
         tnf |       1675    10.44436    .7426236         8.98779    11.90093
         il6 |       1675    329.1224    33.47028        263.4744    394.7704
        il10 |       1675    22.34848    1.679768        19.05381    25.64314

.
.
end of do-file

. do "C:\DOCUME~1\RSITLO\LOCALS~1\Temp\STD010000.tmp"

. clear

.  use "C:\Documents and Settings\RSITLO\Desktop\TOD\fullvalueslogtransformed.dta", clear

.
. bysort fu: ci tnf il6 il10

_____________________________________________________________________________
-> fu = 0

    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
         tnf |        231    13.73117    1.525233        10.72595    16.73638
         il6 |        231    1302.035    575.8675        167.3855    2436.685
        il10 |        231    30.89524    5.131352        20.78477     41.0057

_____________________________________________________________________________
-> fu = 1

    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
         tnf |       1379    10.04511     .793273        8.488952    11.60126
         il6 |       1379    318.4954    33.02788        253.7051    383.2858
        il10 |       1379    21.85975     1.89004        18.15209    25.56742
```

```
-------------------------------------------------------------------------------
-> fu = .

    Variable |        Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+---------------------------------------------------------------
         tnf |        143     12.9021    3.979757        5.034871    20.76932
         il6 |        143    259.7958    56.96867        147.1795    372.4121
        il10 |        143    26.76294    6.316542        14.27633    39.24955


.

.
end of do-file
```

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