Effects of Beta Blockers on Hospital Admission Rates and Cost

Naihui Zhou[1,2,3], Ronald Low[2,3,4], M.D. M.S., Shunsuke Ito[2],M.A.,

Van Dunn[3], M.D., M.P.H

[1]Interdepartmental Program of Bioinformatics and Computational Biology, Iowa State University, Ames, IA and Department of Statistics, Columbia University, New York, New York
[2]New York City Health and Hospitals Corporation, New York, NY
[3] New York City Health and Hospitals Corporation, Metroplus Health Plan, New York, NY
[4]Department of Emergency Medicine, New York University, New York, NY

Abstract

Objective: We study the effect of beta blocker use by New York City MetroPlus health plan patients on hospital admissions and cost.

Methods: To model admissions, we used a zero-inflated negative binomial regression model. We modeled total medical costs with a log linear regression model with Gamma distribution. Medical costs were calculated by summing charges for hospital admissions, clinic and emergency department visits, professional charges, and drug prescriptions paid by insurance. Explanatory variables include comorbidities, gender, age, socioeconomic factors and drug usage.

Results: Beta1-specific blockers with odds ratio of 2.58 (2.13-3.14) and nonselective beta blockers of 1.69 (1.21-2.36) are positively associated with the occurrence of hospital admission (zero inflation component). We did not find interaction effects with COPD or depression. Nor did we find a relationship between beta blocker usage rate of hospital admission regression component). A cost ratio of 1.5376 (1.4197, 1.6652) for beta1 blocker takers and non-takers is found for the COPD population. Increased cost of beta blocker therapy is also significant in depression patients.

Conclusions: We found statistically significant relationship between beta blocker use and lack of hospital admission (zero inflation component), but not with the hospital admission rate among COPD and depression patients. Beta blocker use is associated with higher total cost.

Key words: beta blockers, negative binomial, zero-inflated

1. Introduction

The Institute for Healthcare Improvement and other leaders push the “triple aim” of: 1) improving the patient experience of care, including quality of care 2) improving population health and 3) reducing costs. Improving the integration of care is one proposed mechanism for achieving these goals: treatment for one problem should not exacerbate others. The use of beta blockers has been clinically demonstrated to reduce morbidity and mortality in patients with coronary artery disease, congestive heart failure and hypertension[1]. Beta blockers may also be used to treat glaucoma and dysrhythmias. Beta blockers may exacerbate obstructive lung disease, depression, or other conditions.

Chronic Obstructive Pulmonary Disease (COPD), which includes asthma, is the third leading cause of death in the United States in 2010[2]. The total national medical costs attributable to COPD were estimated at $32.1 billion dollars annually[3]. Underlying pulmonary conditions are also a risk factor for cardiovascular disease[4]. Agonists, particularly beta-2 agonists are widely used as bronchodilators in the

treatment of COPD, including asthma. About 10% of the adult US population suffers a depressive episode in a given year, with costs comparable to COPD[5].

Since beta blockers and bet agonists oppose each other's effects, patients who need beta agonists are usually excluded from clinical trials meant to prove the safety and efficacy of beta blockers. Reflecting this limited data and the theoretical risks, FDA mandated package inserts caution against prescribing beta blockers to patients with asthma or other conditions which could be exacerbated.

Limited research analyzes the effects of beta blockers on: A) respiratory functions of COPD patients[6]. A meta-analysis of randomized clinical trials has shown no reduction in airway function or exacerbation of COPD for patients given cardio selective beta blockers[7]. A survival benefit was found for COPD patients after AMI who are prescribed beta blockers but not beta agonists[8]. B) Depression exacerbation [9, 10]. Prescription of beta-blockers is not significantly associated with an increase in depressive symptoms in the first year after MI [11]; the long-term effects of beta blockers are to be addressed.

This study examines a large group of patients (n=384,002), attempting to understand the effects of beta blockade on hospital admission and cost. We include possible confounding variables to help explain variation. We used generalized linear and zero-inflated regression models.

2. Data

We used de-identified data from the MetroPlus health plan, a New York City medical insurance provider. During a study period from Jan. 1st, 2011 to Feb. 26th 2014, 384,002 patients were enrolled: 7,995,342 records of hospital visits and 829,538 [1] pharmacy claims were recorded.

1.1. Distribution of admissions

As observed in the histogram of number of admitted patients (Figure 1), 85.24% of the patients in our study had zero admission, necessitating the zero-inflated model. Overdispersion (Table 1) suggests that the Negative Binomial regression would fit better and be more robust than a Poisson model.

[1] Only claims including the following classes of drugs are included: ACE inhibitors, Alpha-1 blockers, Antidepressants, ARB inhibitors, Beta agonists, Beta blockers, Diuretics and Glucocorticoid.

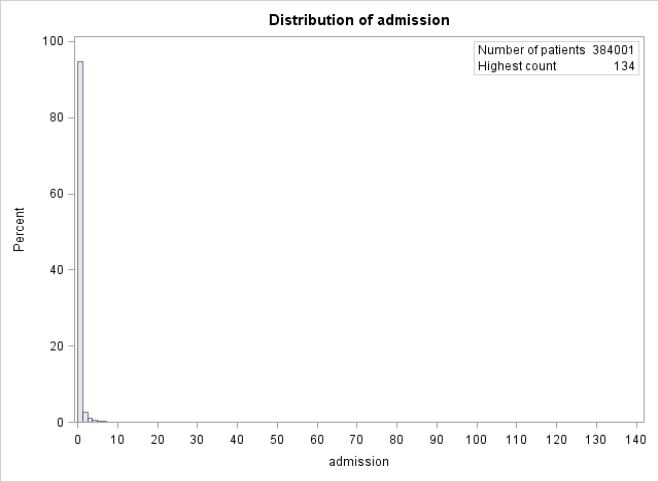

Figure 1: Histogram of Admission

Table 1: Mean and Variance of Admission

	Mean	*Variance*
Admission count	0.3125	2.0871
Zero-truncated admission	2.1174	10.3199

1.2. Distribution of cost

Cost is the total amount paid by MetroPlus including pharmacy, professional and hospital costs during the study period. Only 1.81% beneficiaries had zero cost. Figure 2 is the zero-truncated plot on a log scale of the cost distribution. Gamma distribution has been widely used to model the size of insurance claims. So a fitted gamma curve is plotted in Figure 2.

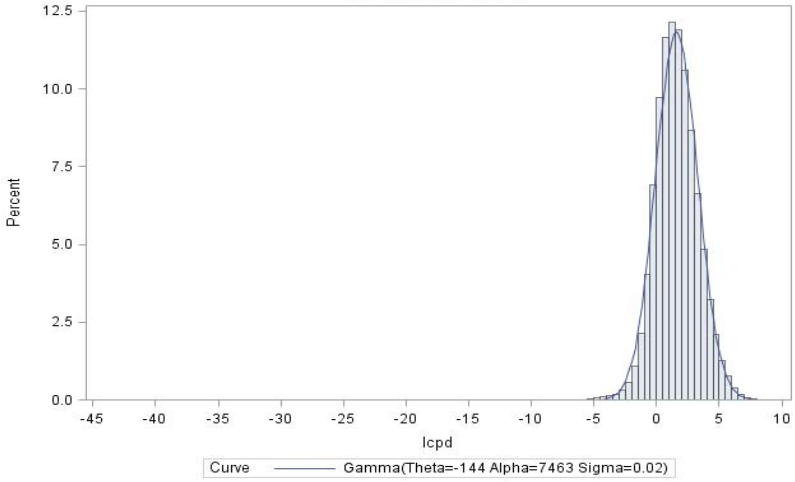

Figure 2: Empirical Distribution of Cost Per Day and fitted Gamma Curve

1.3. Explanatory variables

1.3.1 Comorbidity

Three types of comorbidities are included, first are the clinical conditions included in calculating the Charlson Index[12]. These conditions include: AIDS, myocardial infarction, congestive heart failure (CHF), dementia, cerebral vascular disease, COPD, connective tissue disease, ulcer, mild liver disease, moderate to severe liver disease, diabetes, diabetic complications, hemiplegia, chronic kidney disease, leukemia, malignant tumor, and metastasis.

In addition to the above conditions, we also included disease related to the use of beta blockers. These include indications and contraindications of beta blockers: hypertension, coronary artery disease, dysrhythmia, bradycardia and depression (Episodic mood disorders (ICD9:296-297 and other depression: ICD9:311). We also included all psychiatric comorbidity and a subset of that, schizophrenia. The following table shows these conditions and their respective counts.

Table 2: Second type of comorbidities: conditions related to beta blockers

Conditions	*Count*
Hypertension	92364
Coronary Artery Disease (CAD)	18316
Dysrhythmia	1931
Bradycardia	101
Episodic Mood Disorders	30592
Other Depression	25867
Asthma	81998
Psychiatric Conditions	121669
Schizophrenia	9180

1.3.2 Drugs

Tables 3 shows drug classes of interest, including anti-hypertensive drugs, beta agonists and antidepressants and their respective counts.

Table 3: List of drugs of interest and respective counts

Drug Class	*Count*
Anti-Hypertensive Drugs	
Angiotensin-Converting-Enzyme inhibitor (ACE inhibitor)	40921

Alpha blockers	Alpha1-specific	7515
Angiotensin Receptor Blockers(ARBs)		22227
Beta Blockers	Beta1-specific	27178
	Non-selective	12239
Calcium Channel Blockers	Dihydropyridine	5502
	Non-Dihydropyridine	2694
	Non-selective	28837
Beta Agonists	Beta2 specific	95292
	Non-selective	4785
Antidepressants and Antipsychotics		47465
Diuretics		44932

1.3.3 Age

Age is calculated from date of birth to enrollment effective date. Figure 3 shows the relationship between admission and age. We plot the age by 1-year interval against: A) mean log number of admissions and B) mean log cost/day. Although there is an increasing trend in the number of admission with age, the relationship is not linear and attained a local maximum at approximately ages 45-50.

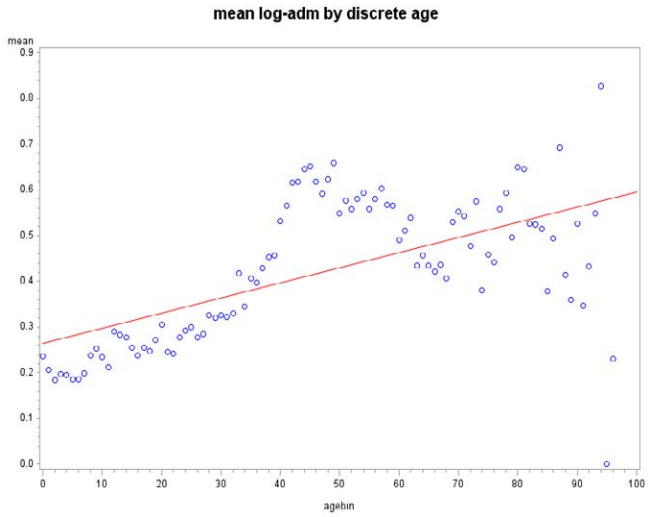

Figure 3: Mean log-transformed admission by discrete age

Therefore, in modeling admission with age, we have divided age into the following groups and created indicator variables.

Table 4: Counts per year

Age Group	*Count*	*Count per year*
0-1	33588	33588
1-17	132411	7789
18-24	34771	4967
25-34	42098	4210
35-44	43778	4378
45-60	75861	4741
61-75	19511	1301
76 and above	1983	N/A

We observed a drop in count at age group 45-60 and 61-75. This may be due to a switch of insurance plan for patients 65 years and older. A separate variable is created for these patients who have dropped out of MetroPlus and switched to Medicare unaffiliated with Metroplus. The cost plot on the right of Figure 3 is smoother than the one on the left, so age as a continuous variable was considered to model total cost.

1.3.4 Socioeconomic factors

We use zip code as a proxy variable for socioeconomic factors. For each zip code area, we have obtained poverty rate and education data from the US Census Bureau. The scatter plot (Figure 4) shows that there's a fair level of correlation between these two variables, r=0.3456.

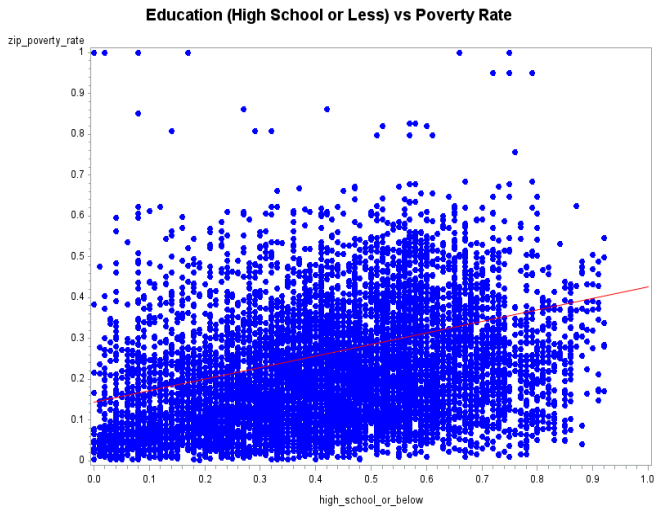

Figure 4: Correlation plot between education and poverty

2. Methods

2.1 Zero-inflated models

Hospital admission can be viewed as count data thus modeled by generalized linear regression with log transformation. Since overdispersion prevents modelling with a Poisson distribution, we considered remedial measures.

Many biometric studies use zero-inflated models[13] to describe count data with an excess of zero's. A zero-inflated model assumes that the population of count data consists of two types of individuals. The first type always gives a zero count, and the second type follows a negative binomial or Poisson distribution with parameter λ and scale parameter k . The probability of an individual being the first type is ω . Both models can depend on covariates.

Since overdispersion is still present after removing the zero counts, a zero-inflated Poisson model is not appropriate[14]. Therefore, we used a zero-inflated negative binomial model.

Then probability distribution of a zero-inflated negative binomial regression of a random variable Y is then given by the following formula.

$$\Pr(Y=y)=\begin{cases}\omega+(1-\omega)(1+k\lambda) & y=0\\ (1-\omega)\dfrac{\Gamma(y+1/k)}{\Gamma(y+1)\Gamma(1/k)}\dfrac{(k\mu)^y}{(1+k\lambda)^{y+1/k}} & y=1,2,\ldots\end{cases}$$

We can estimate the parameters ω and λ by two sets of explanatory variables and .

$$h(\omega_i)=\mathbf{z}_i'^{\blacksquare}$$
$$g(\lambda_i)=\mathbf{x}_\mathbf{i}'$$

where h is the logit link function and g is the log link.

2.2 Gamma regression

Cost can be seen as continuous and therefore is modeled with a Gamma distribution. Cost per day is total cost per patient divided by total days of insurance coverage. Figure 2 showed that distribution of cost per day approximates a gamma distribution.

3. Results

3.1 Admission

We modeled variables that are associated with zero admission as well as numbers of admissions. Criteria for including an explanatory variable are: α=.05, AIC is lower with the term than without it, and the term had to had to have some plausible direct relation to the outcome Two sets of parameters are

estimated for the negative binomial regression and the zero-inflation regression. Age group 25-35 serves as the baseline category for age.

See appendix for full list of estimates and Wald 95% confidence interval.

Table 5: Estimates of coefficients (partial results[2])

Coefficient (S.E.)	*Zero Inflation*	*Negative Binomial*
Beta1 Blocker	0.9491 (0.0996)	-
Beta Blocker NS	0.5250 (0.1704)	-
Beta2 Agonist	0.1823 (0.0547)	0.0416 (0.0188)
Beta Agonist NS	0.9941 (0.1554)	0.4401(0.0425)
COPD	-	0.3763(0.0236)
Asthma	-	0.1371(0.0272)
Episodic Mood Disorders	1.0924 (0.1297)	0.2859(0.0201)
Other Depression	0.4898 (0.099)	0.5271(0.0187)
Hypertension	0.3211 (0.0527)	0.3206(0.0169)
CAD	1.2878 (0.1348)	0.4214(0.02)
Dysrhythmia	2.0917 (0.3417)	0.5862(0.0485)
Episodic Mood Disorders * Beta1 Blocker	-1.4138 (0.3576)	-

Beta1 blockers have a significant effect in predicting hospital admission with an odds ratio of 2.5833 (log odds ratio 0.9491). Patients taking beta blockers are 2.6 times more likely to be admitted (as opposed to not having any admission) than those who are not taking beta1 blockers. However, it is not associated with any increased numbers of admission. Similarly, patients taking beta2 agonists are 1.2 times more likely to be admitted. Even though the negative term for the interaction of episodic mood disorder and beta1 blocker may suggest reduced odds of admission for patients with episodic mood disorder taking beta1 blocker, the sum of parameters for the three respective terms are positive, which indicates increased odds of admission for those patients. However, examining the contrast analysis for patients with episodic mood disorders, the effect of beta1 blocker on odds of admission was not statistically significant.

[2] For a full list of parameter estimates, please contact author (nz2231@columbia.edu).

Beta agonists, COPD and other covariates all have a positive effect on the number of admission. For instance, the mean number of admission for COPD patients is 1.4569 times of that for non-COPD patients, with other variables held constant.

The following table show coefficient estimates of age, gender and zip poverty rate. The reference level for gender is female. Males are less likely to have an admission than females, with an odds ratio of 0.2820. However, males have an average higher rate of admissions than females.

Zip poverty rate predicts reduced admission. This may be attributed to people's avoiding the hospital for financial reasons.

Table 6: Estimates of coefficients of demographic and socioeconomic variables

Coefficient (S.E.)	*Zero Inflation*	*Negative Binomial*
Age group 0-1	-	-0.4347(0.0244)
Age group 2-17	-	-0.6939(0.0262)
Age group 18-24	1.3922 (0.051)	-0.0839 (0.0248)
Age group 35-44	0.4192 (0.0608)	-0.1442 (0.0219)
Age group 45-60	0.5141 (0.0586)	-0.4233 (0.0215)
Age group 61-74	0.3041 (0.0628)	-0.5473(0.0269)
Age group 75 and over	-	-0.1315(0.0529)
Gender	-1.2659 (0.0432)	0.4668 (0.0148)
Zip Poverty Rate	-1.3922 (0.051)	-0.4347 (0.0244)

3.2 Cost

A list of main effects and interactions are identified as associated with increased cost for the insurance company. Table 7 shows the parameter estimates for anti-hypertensive drugs.

Table 7: Parameter estimates for antihypertensive drugs

	Coefficient (S.E.)	*Mean Estimate*	*p-value*
ACE	-0.0995 (0.0088)	0.90529	<.0001
ARB	-0.1285 (0.0107)	0.879414	<.0001
Ca Channel blocker ND	0.0883 (0.0256)	1.092316	0.0006
Ca Channel blocker D	0.1059 (0.0183)	1.111711	<.0001

Alpha1 blocker	0.2351 (0.0266)	1.265035	<.0001
Beta1 blocker	0.3138 (0.0335)	1.368616	<.0001
Beta blocker NS	0.4469 (0.0279)	1.563458	<.0001
Ca Channel NS	-	-	-

ACE inhibitors and ARBs have a negative effect on cost. Patients taking these drugs have less average cost than patients not taking these drugs. Beta blockers generate the largest increase on cost among all anti-hypertensive drugs.

For significant interactions, in-population contrasts estimates are obtained in Table 8.

Table 8: Estimates of specified coefficients given another coefficient

Effect Variable	*Base Variable*	*Estimate (S.E.)*	*Mean Estimate*	*P-value*
Beta1 blockers	Episodic Mood Disorders	0.1181 (0.044)	1.1254	0.0073
Beta blockers NS	Episodic Mood Disorders	0.1638 (0.0473)	1.178	0.0005
Beta1 blockers	Other Depression	0.1426 (0.0438)	1.1532	0.0011
Beta blockers NS	Other Depression	0.1723 (0.0489)	1.188	0.0004
Beta1 blockers	COPD	0.4302 (0.0407)	1.5376	<.0001
Beta blockers NS	Hypertension	0.0691 (0.0129)	1.0715	<.0001
Beta1 blockers	Hypertension	0.1571 (0.024)	1.1702	<.0001
Beta1 blockers	Hypertension AND Beta2 Agonist	-0.0572 (0.0291)	0.9444	0.0493

For patients diagnosed with episodic mood disorders, those taking beta1 blockers or Non-specific beta blockers generate more cost than those not taking the drugs, although beta1-specific has a slight lower estimate than non-specific beta blockers. The same positive effect is also present on COPD patents. The analysis suggests beta blocker usage in hypertension patients would increase mean cost in a small magnitude (cost ratio 1.1702). If beta blockers prevent long term effects of hypertension, this study might not find the benefit due to the relatively short study period. Hypertensive patients taking beta2 agonists already have reduced costs if they start taking beta1 blockers.

4. Discussion

4.1 Reducing admission

In light of the triple aim agenda, hospital admissions are used as one quality measure: hospital admission is expensive, usually an unpleasant patient experience, and may represent a failure of quality outpatient care. Comorbidities such as previous heart attacks, dementia, and malignant tumor are related to increased numbers of hospital admission. Focused care plans for these patients may reduce admissions. Beta blocker use was associated with higher probability of at least one admission. We did not find our anticipated explanation for this relationship: we did not see a significant interactive effect of beta blockers on COPD patients. Our analysis is some evidence that treating hypertension, CAD or dysrhythmia with beta blockers may be safe, even for COPD or depression patients. Our results are consistent with previous research [7, 8], which suggests that beta1 blockers do not have deleterious effects on respiratory functions. We also did not see an increased number of hospital admissions among mood disorder patients taking beta blockers

4.2 Reducing cost

Beta blocker therapy was associated with higher insurance costs, compared to other anti-hypertensive drugs (ACE, ARBs, Alpha blocker and Calcium channel blockers). This may be due to the fact that beta blockers predict non-zero hospital admission while some other anti-hypertensive drugs, ACE and ARBs perfect examples, predict reduced (or zero) hospital admission. Although some beta blocker therapies are not related with increased admission, they are related with increased cost. In patients with mood disorders and COPD, taking beta blocker is predicted to generate more cost than not taking beta blockers. Our experimental unit was one patient, over the entire period of Metroplus enrollment. If the patient was diagnosed with depression at any point, the depression variable was set to "1". Consequently, our model did not allow us to model the probability that depression or COPD became clinically noticeable as an adverse consequence of starting beta blockers or other drug started during the observation period. The magnitude of the increase in cost is lower for beta1 blocker than non-selective beta blocker in depressive patients. Further analysis is called upon to analyze the difference in effect of these two types of beta blockers.

References

1. López-Sendó, J., et al., *Expert consensus document on β-adrenergic receptor blockers The Task Force on Beta-Blockers of the European Society of Cardiology.* European Heart Journal, 2004. **25**(15): p. 1341-1362.
2. Murphy, S.L., J. Xu, and K.D. Kochanek, *Deaths: final data for 2010.* National vital statistics reports, 2013. **61**(4): p. 1-118.
3. Ford, E.S., et al., *TOtal and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged ≥18 years in the united states for 2010 and projections through 2020.* Chest, 2014.
4. Kuller, L.H., et al., *The Epidemiology of Pulmonary Function and COPD Mortality in the Multiple Risk Factor Intervention Trial.* American Review of Respiratory Disease, 1989. **140**(3_pt_2): p. S76-S81.
5. Centers for Disease Control and Prevention, *Workplace Health Promotion Impementation-Depression.* 2013.

6. Hawkins, N.M., et al., *Heart Failure and Chronic Obstructive Pulmonary DiseaseThe Quandary of Beta-Blockers and Beta-Agonists.* Journal of the American College of Cardiology, 2011. **57**(21): p. 2127-2138.
7. Salpeter, S., et al., *Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis.* Respiratory medicine, 2003. **97**(10): p. 1094-1101.
8. Chen, J., et al., *Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma.* Journal of the American College of Cardiology, 2001. **37**(7): p. 1950-1956.
9. Carney, R.M., et al., *Prevalence of major depressive disorder in patients receiving beta-blocker therapy versus other medications.* The American Journal of Medicine, 1987. **83**(2): p. 223-226.
10. Golden, R.N. and D.L. Evans, *Beta-blocker therapy and clinical depression.* The American Journal of Medicine, 1988. **84**(3, Part 1): p. 559-560.
11. van Melle, J.P., et al., *Beta-blockers and depression after myocardial infarction: a multicenter prospective study.* Journal of the American College of Cardiology, 2006. **48**(11): p. 2209-2214.
12. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
13. Lambert, D., *Zero-Inflated Poisson Regression, With an Application to Defects in Manufacturing.* Technometrics, 1992. **34**(1): p. 1-14.
14. Yau, K.K., K. Wang, and A.H. Lee, *Zero-Inflated Negative Binomial Mixed Regression Modeling of Over-Dispersed Count Data with Extra Zeros.* Biometrical Journal, 2003. **45**(4): p. 437-452.