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Tianyu Gao Date

Safety of Administering Pegfilgrastim on the Same Day of Continuously Infused 5-Fluorouracil (5-FU) for Patients with Gastrointestinal (GI) Malignancies: A Retrospective Study

By

Tianyu Gao
Master of Public Health

Biostatistics and Bioinformatics

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By

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Bachelor of Arts
Boston University
2016

Thesis Committee Chair: Zhengjia (Nelson) Chen, PhD
Reader: Michael Kutner, PhD

An abstract of
a thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Safety of Administering Pegfilgrastim on the Same Day of Continuously Infused 5-Fluorouracil (5-FU) for Patients with Gastrointestinal (GI) Malignancies: A Retrospective Study
By Tianyu Gao

Purpose: 5-Fluorouracil (5-FU) is a common agent for treating patients with gastrointestinal (GI) malignancies. The primary objective of this study is to examine the safety of pegfilgrastim administration on the same day of continuous 5-FU infusion in regimens.

Methods: Descriptive analysis was used to describe the demographic and clinical covariates. Risks and 95% confidence intervals were constructed to evaluate the safety of administering pegfilgrastim on the same day of 5-FU for all patients and for patients who received prior chemotherapy. Logistic regression was fitted to examine the risk factors for severe adverse events, including grade 3, grade 4 and febrile neutropenia, hospital admission, dose reduction and treatment delay.

Results: Average age of patients of the study was 60.8. The risk of grade 4 and febrile neutropenia among all patients with GI malignancies was 0.007 (95% CI: 0.001, 0.024) while that for patients with prior chemotherapy was 0.000 since no patients reported experiencing such events. The risk of hospital admission was 0.017 (95% CI: 0.005-0.039) for all patients and the risk of that for patients with prior chemotherapy was 0.001 (95% CI: 0.000-0.053). The odds of grade 3 neutropenia for Caucasians was 0.14 (95% CI: 0.01-1.88) of that for African American.

Conclusion: The risks of adverse events for patients with GI malignancies and for patients who had prior chemotherapy were low. Older patients were likely to have higher odds of experiencing severe adverse events. Racial difference was also observed for grade 3 neutropenia, where African American may have higher odds of experiencing it. Further studies would be needed to examine the effectiveness of administration of pegfilgrastim on the same day of continuous 5-FU infusion for patients with GI malignancies.

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Tianyu Gao

Table of Contents

1. Introduction

Gastrointestinal (GI) cancer is the malignant condition of the digestive system, including esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus (Yamada, et al., 2011). GI cancer is one of the most common types of cancer and represents a major health issue. GI cancer may occur at any age but older people are more susceptible to it and the prevalence of GI cancer is higher among males. Taking stomach cancer as an example, the average age of the cancer diagnosis is 68 and approximately 26,240 will be diagnosed of this type of cancer in the United States in 2018, estimated by American Cancer Society (American Cancer Society, 2018).

Neutropenia, a common side effect of chemotherapy, refers to the presence of abnormally low neutrophils in blood and will consequently increase the risk of infection in patients (Bodey, Buckley, Sathe, & Freireich, 1996). Febrile neutropenia refers to the presence of low blood neutrophils with high body temperature (Kuderer, Dale, Crawford, Cosler, & Lyman, 2006). 5-Fluorouracil (5-FU) continuous infusion is a common therapeutic agent for treating early and late stage of GI malignancies (Tan & Ang, 1996). 5-FU is indicated to have a low risk of neutropenia but may have higher risks with other agents combined.

Filgrastim is a recombinant granulocyte colony-stimulating factor (G-CSF) that can stimulate the hematopoiesis of the granulocyte system, promote the proliferation of neutrophils and decrease the incidence of infections. It is used to maintain dose intensity and the density of receiving myelosuppressive chemotherapy. Pegfilgrastim (Neulasta) is a pegylated long-acting recombinant growth factor that has a similar mechanism neutropenia but with a long-acting effect than filgrastim (Holmes, et al., 2002). It is

indicated to decrease the incidence of infection, manifested by febrile neutropenia, when administered after 24 hours of chemotherapy. Unlike filgrastim that has to be injected daily, pegfilgrastim allows patients to inject only once per chemotherapy cycle (Green, et al., 2003). Pegfilgrastim is recommended not to be administered within 14 days before and after 24 hours of chemotherapy because myeloid progenitors cells induced by G-CSF are sensitive to chemotherapy. However, for patients with GI malignancies receiving continuous 5-FU, pegfilgrastim administration may increase the risk of neutropenia. Hence, earlier administration of pegfilgrastim may be less of a concern for such patients as the half-life of 5-FU is 8-14 minutes.

There were studies that have done an evaluation of the performance of pegfilgrastim for patients receiving chemotherapy. Burris et al have done a study on assess pegfilgrastim on the same day versus next day of chemotherapy for patients with breast cancer, lung cancer, ovarian cancer and non-Hodgkin's lymphoma (Burris, et al., 2010). Another study has done by Linot et al on determining the efficacy and safety of early G-CSF administration in patients with head and neck cancer treated by docetaxel-cisplatin and 5-FU (Linot, Augereau, Breheret, Laccourreye, & Capitain, 2014). There was also a study done to assess the effectiveness and safety of same-day versus next-day administration of G-CSF for prevention of chemotherapy-induced neutropenia (Lyman, et al., 2017). However, no trials have been done for patients with GI malignancies.

This study evaluates the performance of pegfilgrastim for patients with GI malignancies by measuring the risk of neutropenia by constructing logistic regression models. The

primary objective is to determine the safety of pegfilgrastim administration on the same day of continuous 5-FU for patients with GI malignancies and for patients receiving cytotoxic chemotherapy every 2 weeks.

2. Patients and Methods

2.1 Study Design

Patients with GI malignancies were enrolled in the study. Patients were eligible to participate if they were 18 years or older with adequate renal and liver function. Patients who had an active infection and who were pregnant were excluded from the study. All medications taken by participants were reviewed and evaluated by a physician to determine if they affect the participants' eligibility to participate in the study and the safety variables were frequently used to assess the effectiveness of the pegfilgrastim injection under development and on the market. And all patients provided written informed consent before the study.

This randomized, open-label study was conducted in 300 patients with GI malignancies. There was a fourteen-day period between each dose. The participants received regimens consisting of continuously infused fluorouracil every two weeks and received pegfilgrastim on the same day of 5-Fluoruracil pump disconnected via query of treating oncologists at Emory University Winship Cancer Institute and a report using electronic medical record at Georgia Cancer Center for Excellence at Grady Health System. Complete blood count was collected on the last day of 5-Fluoruracil pump and then every

two weeks for each cycle. Patients from January 2010 to May 2017 were enrolled in the study retrospectively.

Demographics, patients' characteristics and disease history were obtained for all participants including: age, race, gender, cancer diagnosis, disease stage, number of prior treatments, absolute neutrophil count (ANC) prior to each cycle of chemotherapy, lowest neutrophil count recorded per cycle, number of dose reductions, number of dose delays, and number of febrile neutropenic episodes, number of hospital admissions for febrile neutropenia. Grade 3 neutropenia was defined if ANC was within 500 to 1000 cells/mm^3 and grade 4 neutropenia was defined if ANC was smaller than 500 cells/mm^3. Febrile neutropenia was defined if ANC was smaller than 500 cells/mm^3 or an ANC that is expected to drop to <500 cells/mm^3 during two days with body temperature >38.3 Celsius degrees or >38 Celsius degrees that lasted longer than an hour.

2.2 Statistical Analysis

2.2.1 Descriptive Summarization

The descriptive analysis was constructed in the beginning to provide a basic understanding of patients' characteristics. Means and standard deviations were used to describe continuous variables. Frequencies and percentages were used to describe binary and categorical variables (**Table 1**.). Chi-square tests were conducted for binary and categorical variables to assess the between-group differences and P-values were reported in **Table 1**.

2.2.2 Risk Analysis

Absolute risks, measuring the probability of certain events occurring in a group, and 95% confidence intervals were then conducted for outcome variables, which are grade 3 neutropenia, grade 4 neutropenia, treatment delay due to neutropenia, treatment reduction due to neutropenia, febrile neutropenia, and hospital admission (**Table 2**.). Confidence intervals (also called Clopper-Pearson intervals) were computed by the binomial exact method because the calculation was based on the cumulative probabilities of the binomial distribution instead of approximation to binomial distribution (Clopper & Pearson, 1934). The formula of the Clopper-Pearson interval is

$$\frac{1}{1+\frac{n-x-1}{x}F_{2(n-x+1),2x,\frac{\alpha}{2}}} \leq p \leq \frac{\frac{x+1}{n-x}F_{2(x+1),2(n-x),\frac{\alpha}{2}}}{1+\frac{x+1}{n-x}F_{2(x+1),2(n-x),\frac{\alpha}{2}}},$$

where n is the total number of patients in this case, x is the number of times an event occurs at least once, α is the level of significance and $F_{2(x+1),2(n-x),\frac{\alpha}{2}}$ is the $\frac{\alpha}{2}$th percentile of the F distribution with 2(x+1) and 2(n-x) degrees of freedom (Clopper & Pearson, 1934).

2.2.3 Logistic Regression

Variables that were significant at baseline were included in the logistic models. Race were recoded to Caucasian, African American and other since there was little information about other racial groups. Because all observations of bone marrow involvement, persistent neutropenia had the same level, variable prior chemotherapy, prior radiotherapy, persistent neutropenia, bone marrow involvement, major surgery within 6 weeks, bili >2 micromol/L, and CrCl <50 mL/minute were considered as risk factors and

combined to one numeric variable. Variable cancer diagnosis, stage of diagnosis, reason for neulasta were treated as categorical variables. Since we want to model the probabilities of the outcome variables as a function of explanatory variables, logistic regressions were fitted. For a binary response variable Y and a vector of explanatory variables X, the response probability can be expressed as

$$\pi_i = P(Y_i = 1|X_i) = \frac{e^{\beta x_i}}{1+e^{\beta x_i}} = \frac{1}{1+e^{-\beta x_i}}.$$

Then the linear logistic model has the form

$$\text{logit}(\pi_i) = \log\left(\frac{\pi}{1-\pi}\right) = \beta' x_i ,$$

where β_0 is the intercept parameter and $\beta = (\beta_1, \dots, \beta_k)'$ is the vector of k slope parameters (Agresti, 2002). The parameter estimates were typically fit using maximum likelihood estimation, which means the parametric likelihood below is maximized as a function of β (Agresti, 2002; Walker & Duncan, 1967).

$$L(\beta|Y,X) = log \prod_i \frac{e^{y_i \cdot \beta' x_i}}{1+e^{\beta' x_i}} = \sum_{i:\, Y_i=1} \beta' x_i - \sum_i \log(1 + e^{\beta' x_i}).$$

The score function, also known as the gradient of the log-likelihood function, is

$$U(\beta) = \frac{\partial}{\partial \beta} L(\beta|Y,X) = \sum_i (y_i - \pi_i) x_i.$$

However, if the outcome had low prevalence in logistic regression models, the estimated coefficients may be biased and all observations would have the same event status. This phenomenon is known as “separation” (Firth, 1993). One way to address the separation problem is to use Firth’s (1993) bias-adjusted estimates. The Firth penalized method is useful when facing rare events and is an alternative approach to performing an exact

logistic regression (Heinze & Puhr, 2010). The Firth method replaces the usual score function with a modified one, which is

$$U(\beta) = \sum_i [y_i - \pi_i + h_i\left(\frac{1}{2} - \pi_i\right)]x_i \ ,$$

where the h_i's are the ith diagonal elements of the hat matrix $H = W^{\frac{1}{2}}X(X'WX)^{-1}X'W^{\frac{1}{2}}$ and $W = diag\{\pi_i(1-\pi_i)\}$ (King & Zeng, 2001).

Last but not the least, backward selection was applied to select the model based on Akaike Information Criterion (AIC) and P-values. AIC is an index for estimating the quality of statistical models within a given dataset. It estimates how close the fitted values tend to be true values for a model and it assesses the tradeoff between the simplicity and goodness of fit of the model. Let $\hat{L}$ be the maximum value for the likelihood function for a model, AIC can be written as

$$AIC = 2k - 2\ln(\hat{L}) \ ,$$

where k is the number of covariates in the model (Aho, DeWayne, & Teri, 2014; Akaike, 1998). The type 3 analysis of effects test was used to test the significance of the covariate and the Wald test was used to test the significance of the overall model. The lower the value of AIC, the better the model. Because the level of significance was considered as 0.05 in this thesis, P-values lower than 0.05 indicates statistically significant models. Then odds ratio was calculated by using the final models for examine model effects.

All patients who received the study drug were included in the safety analyses and patient identifiers were removed by the investigators before the analysis. All of the data cleaning, management and analyses including Chi-square test, Firth penalized logistic regression,

AIC, and likelihood ratio test were done in SAS 9.4 (SAS Institute, www.sas.com) and R 3.4.3 (The R Foundation for Statistical Computing, www.r-project.org). Level of significance was set to 0.05 in all analyses.

3. Results (See Appendix)

3.1 Descriptive Summarization

A total of 300 patients who fulfilled the inclusion criteria were included. The demographic information was summarized in **Table 1**. From the table, the average age of GI malignances patients participated in the study was 60.8 (standard deviation = 9.3). Most patients were in the low risk group (≤65: 69.0%) and a large proportion of patients had metastatic disease (77.0%). Caucasians were the majority (51.0%), followed by African Americans (37.7%) and Asians (4.3%). No patients had bone marrow involvements. And almost all patients never had persistent neutropenia and never undergone major surgery within six weeks of the study. There were no significant differences between gender (P-value = 0.06) while all other demographic or baseline characteristics were statistically significant (P-values ≤ 0.001).

3.2 Risk Analysis

Three patients developed grade 3 neutropenia and two patients developed grade 4 neutropenia. Among them, no one had the event more than once. However, among patients who developed febrile neutropenia, one had the event more than once and the other one only had it for once. As shown in **Table 2**, the risk of having grade 3 neutropenia is 0.010 (95% CI: 0.002-0.029), whereas the risks of grade 4 neutropenia and

febrile neutropenia were 0.007 (95% CI: 0.001-0.034). The risk of hospital admission was the highest at 0.017 (95% CI: 0.005-0.039).

There was a total of 103 patients who received chemotherapy. Among them, no one developed grade 3 and grade 4 or febrile neutropenia (95% CI: 0.000-0.035). Two subjects had treatment delay due to neutropenia (95% CI: 0.002, 0.068). And the risk of hospital admission was 0.001 (95% CI: 0.000-0.053). As shown in **Figure 1**, the risk of hospital admission was the highest among all patients with GI malignancies and the risk of treatment delay was the highest among patients with prior chemotherapy.

3.3 Univariable and Multivariable Logistic Regression Analysis

Univariable logistic regressions of baseline variables were first computed for each outcome variable, including grade 3 neutropenia, grade 4 neutropenia, febrile neutropenia and hospital admission. With all variables that were significant at baseline included in the model for analyzing grade 3 neutropenia, the variable with the largest P-value was dropped (AIC: 36.76, P-value: 0.29). By backward selection based on AIC and P-values, the final model included the following variables: treatment location, race, cancer diagnosis, stage and number of risk factors and an interaction term of age and number of prior treatment regimens (AIC: 23.33, P-value: 0.012) and is given as

$$logit = -3.31 - 0.89(Location) - 1.36(Race_1) + 0.72(Race_2) + 1.02(Cancer_1) - 2.49(Cancer_2) + 0.90(Cancer_3) + 1.15(Stage) - 1.99(Risk\ factors) + 0.01(Age) \times (Prior\ treatment),$$

where $Race_1$ represented Caucasian, $Race_2$ represented African American, $Cancer_1$ was colorectal cancer, $Cancer_2$ was pancreatic cancer, and $Cancer_3$ was gastric cancer. The residual plots showed the model assumption was correct and the variability of residuals were approximately constant (**Figure 2**). From **Table 4**, the odds of grade 3 neutropenia for Caucasian is 0.86 (95% CI: 0.010, 1.88) less than that for African American.

The final model for grade 4 neutropenia included: age, number of prior treatment regimens and number of risk factors (AIC: 14.81, P-value = 0.023) and is given as

$$logit = -19.37 + 0.23(Age) - 1.60(Risk\ factors) + 1.13(Prior\ treatment\ regimens).$$

The final model of febrile neutropenia was the same as that for grade 4 neutropenia. As shown in **Figure 3**, the model assumption was correct with several positive extreme values. From **Table 5**, with one-year increase in age, the odds of grade 4 and febrile neutropenia would increase by 1.26 (95% CI: 1.05-1.51).

And the best fitted model for analyzing hospital admission involved age and gender (AIC: 41.95, p-value: 0.052) and is given as

$$logit = -9.46 + 0.09(Age) + 0.67(Gender).$$

From the odds ratio estimation, the odds of hospital admission for male patients is 3.84 (95% CI: 0.63-23.45) to the odds for females (**Table 6**).

4. Discussion and Conclusions

In general, patients who experienced serious adverse events in the study were mainly those who had higher number of risk factors. However, the risks of having adverse events

were low and the risks of recurring adverse events were even lower with only one patient experiencing febrile neutropenia more than once and being admitted into the hospital more than once. The logistic models for grade 4 and febrile neutropenia were the same because patients reported grade 4 neutropenia also reported febrile neutropenia with no other patients experiencing these two events. There was a racial difference of receiving grade 3 neutropenia, where African American had a higher risk. For grade 4 and febrile neutropenia, and hospital admission, the older the patients, the higher the odds of the severe adverse events.

The limitation of this study is that a sample size of 300 patients was relatively small in the case of rare adverse events, although the sample size of similar cancer clinical trial data is typically relatively small. Therefore, statistical power for detecting interactions was low and that affected the likelihood of them to be included in the model. Because of the adverse events were rare among all patients, some of the test results may not be accurately assessed.

In conclusion, the study suggests administering pegfilgrastim injection, for patients with GI malignancies, on the same day of continuously infused fluorouracil (5FU) has low risks of grade 3, grade 4 and febrile neutropenia. The risks for patients with prior chemotherapy is even lower. Nevertheless, further studies are needed to validate the effectiveness of administration of pegfilgrastim on the final day of continuous 5-FU infusion for patients with GI malignancies.

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6. Appendix: Figures and Tables

Figure 1. Risks of Severe Adverse Events for All Patients and Patients with Prior Chemotherapy

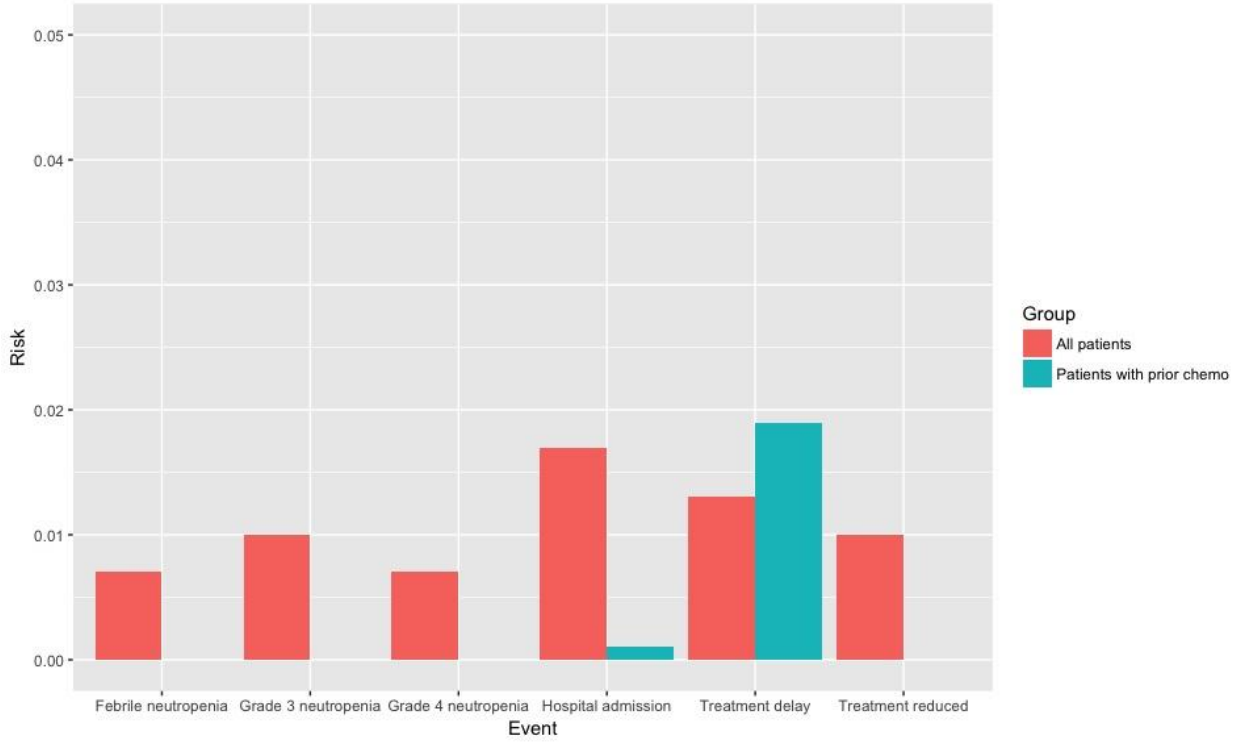

Figure 2. Diagnosis Plots for Grade 3 Neutropenia

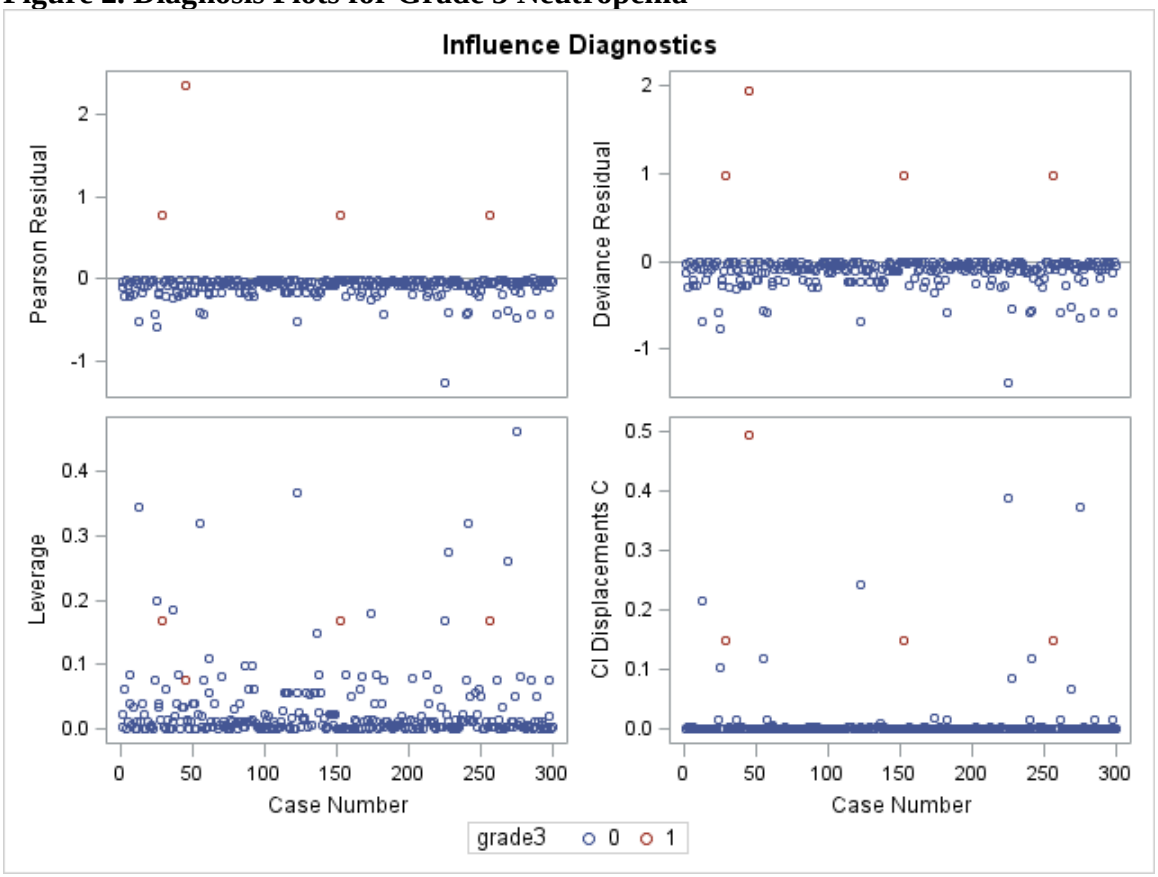

Figure 3. Diagnosis Plots for Grade 4 and Febrile Neutropenia

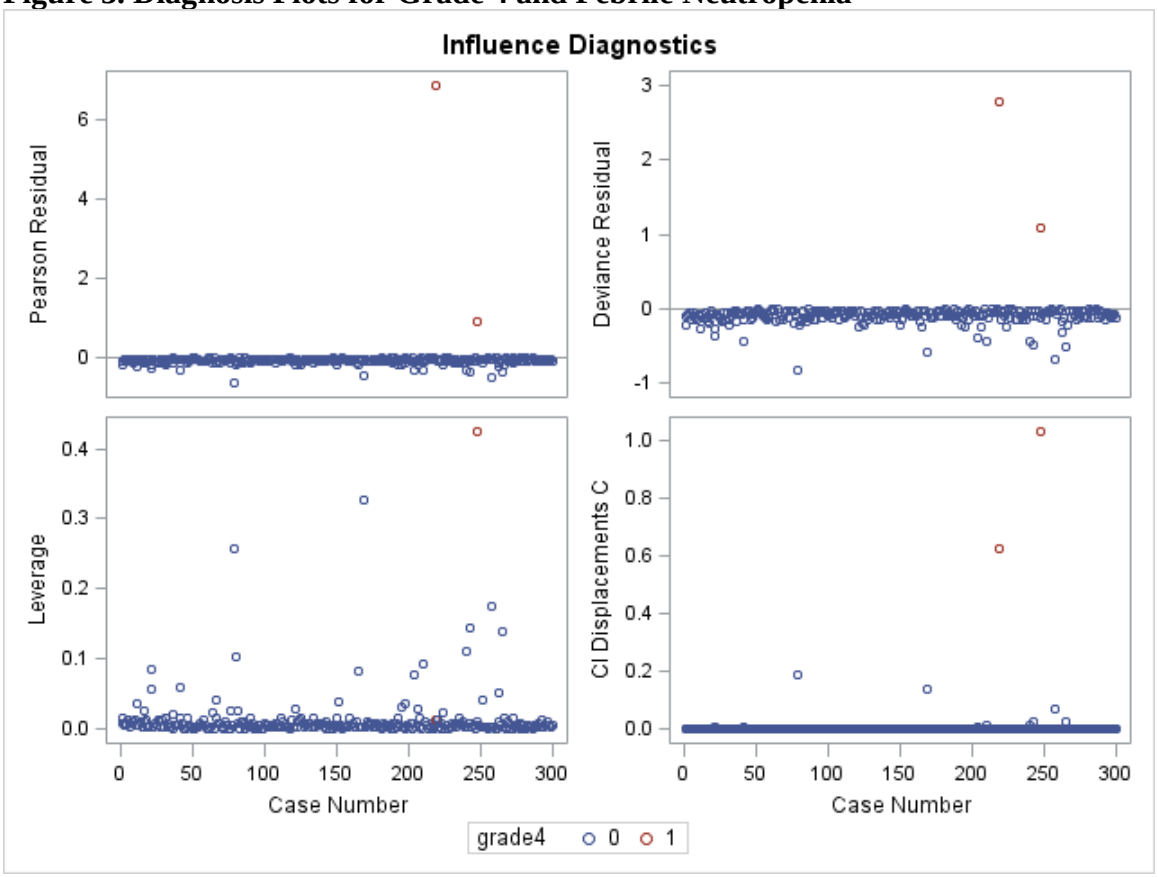

Figure 4. Diagnosis Plots for Hospital Admission

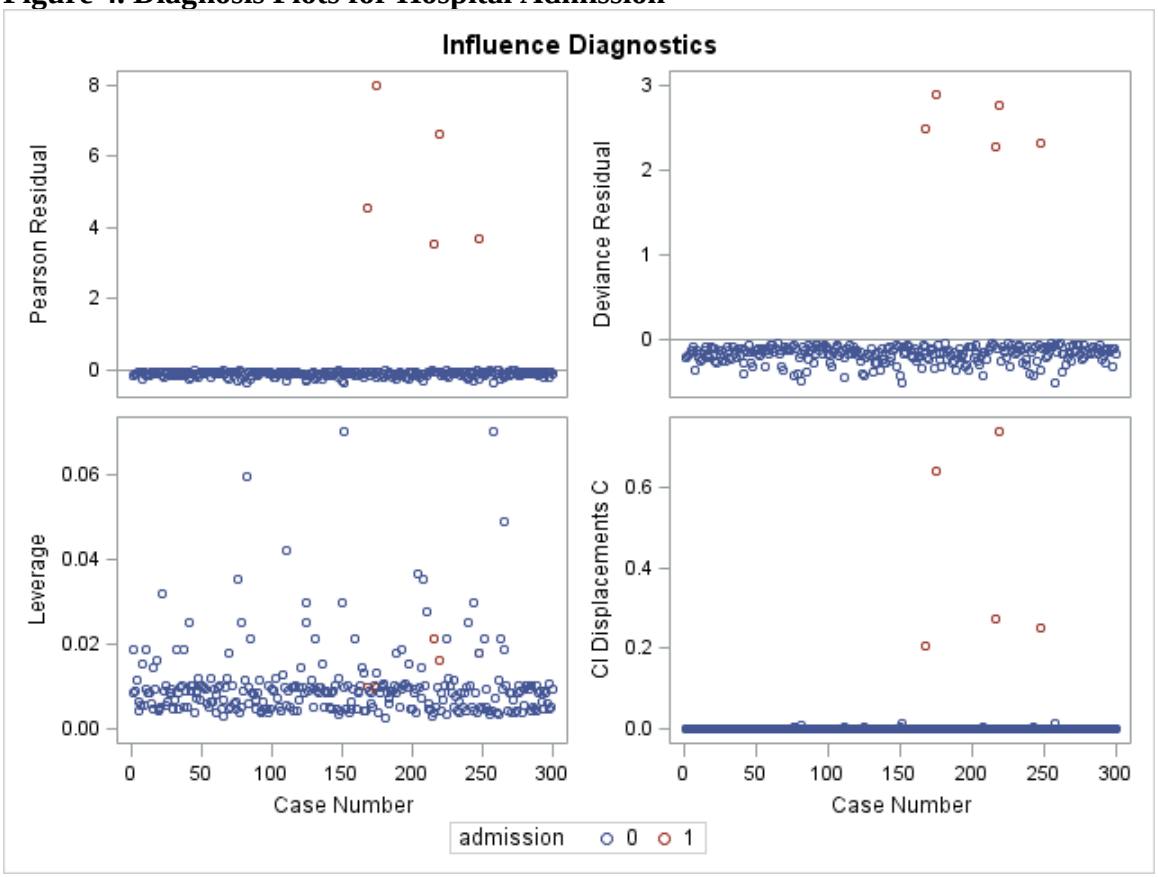

Table 1. Demographic and Baseline Characteristics of Patients

Variable	Level	Statistic (N = 300)	P-value
Tx Location	Emory	264 (12.0%)	<0.0001
	Grady	36 (88.0%)	
Age	-	60.8 (9.3)	
	≤65	207 (69.0%)	<0.0001
	>65	93 (31.0%)	
Race	Caucasian	153 (51.0%)	<0.0001
	African American	113 (37.7%)	
	Asian	13 (4.3%)	
	Hispanic	6 (2.0%)	
	Other	15 (5.0%)	
Gender	Male	134 (44.7%)	0.06
	Female	166 (55.3%)	
Cancer Diagnosis	CRC	74 (24.7%)	<0.0001
	PAN	181 (60.3%)	
	GAS	16 (5.3%)	
	Other	29 (9.7%)	
Stage	Early Stage	69 (23.0%)	<0.0001
	Metastatic Disease	231 (77.0%)	
Reason for Neulasta	Prior FN	7 (2.3%)	<0.0001
	Prior Neutropenic Event	110 (36.7%)	
	Clinical Detection for Upfront Therapy	183 (61.0%)	
Number of Prior Tx Regimens	-	0.58 (1.00)	-
Prior Tx Regimens	Yes	108 (36.0%)	<0.0001
	No	192 (64.0%)	
Prior Chemotherapy	Yes	103 (34.3%)	<0.0001
	No	197 (65.7%)	
Prior Radiation Tx	Yes	39 (13.0%)	<0.0001
	No	261 (87.0%)	
Persistent Neutropenia	Yes	1 (0.3%)	<0.0001
	No	299 (99.7%)	
Bone Marrow Involvement	No	300 (100%)	-
Major Surgery ≤6 Weeks from Start of Therapy	Yes	1 (0.3%)	<0.0001
	No	299 (99.7%)	
Bilirubin >2	Yes	10 (3.3%)	<0.0001
	No	290 (96.7%)	
Creatinine <50	Yes	8 (2.7%)	<0.0001

Clearance	No	292 (97.3%)	
Number of Risk Factors	-	0.85 (0.88)	-
	Yes	177 (59.0%)	0.001
	No	123 (41.0%)	

Table 2. Risk Estimation

Variable	Number of Events	Total Number of Patients	Relative Risk	95% Confidence Interval
Grade 3 Neutropenia	3	300	0.010	(0.002, 0.029)
Grade 4 Neutropenia	2	300	0.007	(0.001, 0.024)
Treatment Delay due to Neutropenia	4	300	0.013	(0.004, 0.034)
Treatment Reduced due to Neutropenia	3	300	0.010	(0.002, 0.029)
Febrile Neutropenia	2	300	0.007	(0.001, 0.024)
Hospital Admission	5	300	0.017	(0.005, 0.039)

Table 3. Risk Estimation for Patients with Chemotherapy

Variable	Number of Events	Total Number of Patients	Relative Risk	95% Confidence Interval
Grade 3 Neutropenia	0	103	0.000	(0.000, 0.035)
Grade 4 Neutropenia	0	103	0.000	(0.000, 0.035)
Treatment Delay due to Neutropenia	2	103	0.019	(0.002, 0.068)
Treatment Reduced due to Neutropenia	0	103	0.000	(0.000, 0.035)
Febrile Neutropenia	0	103	0.000	(0.000, 0.035)
Hospital Admission	1	103	0.001	(0.000, 0.053)

Table 4. Odds Ratio Estimates for Grade 3 Neutropenia

Variable	Level	Odds Ratio (95% Confidence Interval)
Tx Location	Emory	0.17 (0.009, 2.95)
	Grady	Reference
Race	Caucasian	0.14 (0.010, 1.88)
	African American	Reference
	Other	0.91 (0.051, 16.32)
Stage	Early Stage	8.98 (1.40, 57.57)
	Metastatic	Reference
Risk factors	-	0.208 (0.036, 1.18)

Table 5. Odds Ratio Estimates for Grade 4 Neutropenia and Febrile Neutropenia

Variable	Level	Odds Ratio (95% Confidence Interval)
Age	-	1.26 (1.05, 1.51)
Risk factors	-	0.20 (0.03, 1.45)
Prior treatment regimens	-	3.11 (1.36, 7.10)

Table 6. Odds Ratio Estimates for Hospital Admission

Variable	Level	Odds Ratio (95% Confidence Interval)
Age	-	1.09 (0.99, 1.20)
Gender	Male	3.84 (0.63, 23.45)
	Female	Reference