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Adverse Outcomes Associated with Beers List Medications Following Total Knee Replacement

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Abstract

Adverse Outcomes Associated with Beers List Medications Following Total Knee Replacement

By Mofei Liu

Background: Total knee replacement surgery (TKA) is frequently conducted to relieve the symptoms of advanced arthritis of the joint in the past few decades. Although TKA is a highly successful procedure, it can still lead to adverse events, such as readmission, reoperation, emergency room (ER) visit, mortality, and longer length of stay in hospital. Besides other factors contributing to the complication, use of Beers drug could also be a contributor. Beers list is a list of medications that are potentially inappropriate for aged population. In 2015, American Geriatrics Society divided the Beers medications into three categories, Beers 0 (medications that should be used with caution), Beers 1 (medications that should be avoided in all older adults), and Beers 2 (medications that should be avoided in older adults with certain medical condition).

Objectives: In this study, we aim to characterize the usage of three Beers medications in TKA operations performed in the VA health system from 2010 to 2014. We also want to examine the association between the usage of Beers medication and the adverse events (readmission, reoperation, ER visit, mortality, and length of stay in hospital).

Methods: Statistical control chart was used to examine the trend of the three Beers medications over the years. For binary complications (readmission, reoperation, ER visit and mortality), logistic regression was used to detect association with Beer drug dose count after controlling for other clinically interested covariates. The length of stay in hospital was analyzed using multiple linear regression.

Results: Beers 0 has a significant increasing trend in the usage over the 5-year study, while Beers 1 and 2 don't. Beers 1 dose count is significantly associated with readmission within 30 days (OR= 1.03, p= 0.0415) and 90 days (OR= 1.02, p= 0.0409), as well as ER visit within 72h (OR= 1.05, p= 0.0159), within 7 days (OR= 1.04, p= 0.0013), and within 30 days (OR= 1.04, p< 0.001). Beers 2 dose count is significantly associated with ER visit within 72h (OR= 1.24, p= 0.0053), within 7 days (OR= 1.14, p= 0.0113), and within 30 days (OR= 1.09, p= 0.0286). The dose counts of the three Beers medications are associated with the length of stay, among which, Beers 0 has negative association with length of stay (estimate= -0.06, p= 0.0122), while Beers 1 and 2 have positive association (estimate= 0.04, p<0.001 and estimate= 0.14, p<0.001 for Beers 1 and 2 respectively).

Conclusion: The use of Beers 0 has an increasing trend over years while that of Beers 2 and 1 are fairly stable. Beers 1 increases the risk of readmission and ER visit. Beers 2 increases the risk of ER visits. All three categories can significantly contribute to the length of stay in hospital. One dose increase of Beers 0 leads to 1.53 hours shorter while one dose of Beers 1 and Beers 2 leads to 0.72 hour and 1.68 hours longer, respectively.

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Chapter 1

Introduction

The Department of Veterans Affairs (VA) is the largest health care delivery system in the US [1].In 2014, over 6 million patients were enrolled by VA medical center [2], and it formed large databases which have been used in many high-quality scientific researches and studies [1] such as Total Knee Arthroplasties.

1.1 Total Knee Arthroplasties (TKA)

Knee Osterarthritis (OA) is one of the most common disease in the elderly population which can cause severe pain and affect knee function [3]. Total knee surgery (TKA) is frequently conducted in the past few decades to relieve the symptoms of advanced arthritis of the joint and is well accepted by patients to make their knees back to function [4, 5, 6]. Studies have shown that there is an increase of prevalence, in 2020 about 1,375,574 knee replacement surgeries to be conducted in the U.S. [4] [7].

According to Dr.Gene Dossett, chief of orthopedic surgery at the Phoenix VA Health Care System, roughly twenty percent of patients are dissatisfied with the surgery result because of persistent pain after the replacement [8]. Along with other potential risks such as blood loss, prosthetic joint infection, thromboembolism, etc, they lead to substantial costs, need of rehabilitation and longer time stay in hospital [3]. Although TKA is established and highly successful treatment for OA, potential risks can also lead to readmission, reoperation, emergency room (ER) visit and mortality.

1.2 Beers List Drug

One potential contributor to the risks of TKA is potentially inappropriate medications (PIMs), which for older adults are defined as medications with potential risk outweighing the potential benefit and a good alternative drug available [9]. PIMs can carry an increased risk of adverse drug event (ADE) in TKA patient group [10]. A study in the US Emergency Department (ED) showed that about 34.5% (95% CI, 30.3%-38.8%) of Emergency Department (ED) visits are for ADE occurred in people older than 65 [11].

Older people tend to have more diseases as well as altered pharmacokinetics and pharmacodynamics [10], thus they need more medication and longer time to eliminate drugs. The US and Australia investigators discovered that at least one in two people over 65 use five or more prescriptions, and the number of prescriptions is positively associated with age [12]. Increased use of medication may or may not be appropriate depending on the pharmacological effects and potential adverse event [10] [13]. Careful consideration is needed on drug type, dose, and combination to maximum benefit/risk ratio.

To address on this problem, in 1991, Beers and his colleagues developed a criteria for potentially inappropriate medications for elderly population who are over 65 years old, which is a very helpful tool for prescriptions to aged people [13]. Although Beers Criterion was created for nursing home population at first, it became popular among other institutions later on [14]. After several updates, American Geriatrics Society divided listed drugs into several categories, including medications that should be avoided in all older adults, medications that should be avoided in older adults with certain medical condition, and medications that should be used with caution, in 2015. [15].

1.3 Aim of Study

PIMs commonly exist in treatments although Beers criteria listed medications that are inappropriate for older people. Dr. Davidoff et al showed in a study that 42.6% older adults with prescription medications had at least one medication meeting PMI definition [16]. No previous studies have examined the relationship of the use of Beers medication and ADE in Total Knee Replacement surgery. In this study, we quantified the association between Beers drug use and ADE represented by Length of stay in hospital (LOS), readmission, reoperation, emergency room (ER) visit and mortality.

Chapter 2

Method

2.1 Data extraction

The dataset is extracted from VA Health System national corporate data warehouse (CDW) for patients treated with knee replacement surgery from January 2010 through December 2014.

In this study, we used data of patients who were enrolled for the purpose of primary total knee replacement (CPT code 27447), which indicated medial and lateral compartments with or without patella. After data cleaning, 12639 patients from 46 centers were included.

Length of stay in the hospital after surgery for each patient and numbers of different complications (readmission, reoperation, mortality and ER visit) at different times were recorded. Readmission was determined by reviewing descriptions at 30 days and 90 days after the date of surgery. If patients came back for reoperation or occurred death associated with TKA, data was categorized into those occurring within 30 days, 90 days and 365 days after the date of surgery. Reoperation refers to another surgery on the ipsilateral knee. However, if a patient came back for a contralateral procedure or procedure for another part, it's not counted as reoperation. For emergency room visit, we recorded times within 72h, 7 days and 30 days after initial discharge date.

Charlson comorbidity score was created for each patient according to the outpatient problem list and lab data from four weeks before to the date of surgery. We used ICD-9 codes to identify and generate Charlson comorbidity score, which ranges from 0 to 18. A higher score represents more comorbidities.

American Society of Anesthesiologists (ASA) score is to access patients' preanesthesia medical comorbidities. The range of ASA score is 1 (healthy patient), 2 (patient with mild systemic disease), 3 (patient with severe systemic disease) and 4 (patient with severe systemic disease that is a constant threat to life).

2.2 Data cleaning and filtering

We divided the Beers List drug into three subgroups: Beers 0 – medications to be used with caution, Beers 1 – medications to be avoided in older adults, and Beers 2 – medications to be avoided in older adults with specified comorbid conditions. The total dose count of three Beers groups was recorded in the dataset. We excluded several medications of Beers 1 group because we were unable to assure that they meet the requirement of appropriate use, including digoxin, dronedarone, amiodarone, and clonidine. Several drugs exist in both Beers 1 (avoid in all older adults) and Beers 2 (avoid in older adults with specified comorbid conditions), and in this case, we regarded them as Beers 1. In Beers 2 group, we excluded the dose of insulin that was used in conjunction with basal insulin during the same hospitalization without mentioning a sliding scale in the order comments. Sliding scale is determined by keywords such as "sliding," "scale," "correctional," "adjustment," or "sensitivity ratio".

The VA dataset included patients with various purposes for TKA, such as primary total knee replacement, simultaneous bilateral knee replacement, revisions, etc. We excluded patients whose purpose was not primary total knee replacement (CPT code 27486, 27487 and 27488). Procedure description was also manually reviewed to remove patients with a purpose for bilateral, possible unilateral, partial arthroplasty, deformity, removal of hardware, TKA with an additional procedure, and procedure that was not a TKA.

We only selected clinical relevant variables to analyze such as total dose count (Beers 0, Beers 1 and Beers2), number of complications (readmission, reoperation, mortality and ER visit), medical center, length of procedure, American Society of Anesthesiologists (ASA) score, type of anesthesia, VA facility number where the surgery was performed, attending physician unique identifier, admission date and discharge date.

We recorded four complications as binary outcomes, occurred or not occurred. And these new binary outcomes will be used in later data analysis.

We excluded patients with a BMI less than 12 kg/m2 and surgery duration less than 0.75h or greater than 4h, which are likely to be data entry errors. We also excluded one person with an ASA score of "L" because group size is too small for data analysis purposes.

2.3 Data analysis

We used statistical control charts to explore the trend of dose-count used on patients over five years of the study period [17]. Three standard deviations from the overall mean for each quarter were set to be the control limit. Seven or more consecutive values on the same side of mean were regarded as lacking evidence of random distribution, and a trend may exist. Length of stay in the hospital is a very important indicator of the surgery effect. Linear regression was used to analyze the effect of dose-count on the length of stay controlling other covariates. And since there are a number of outliers, robust linear regression was used to control outlier effect.

We focused on the effect of the dose count of three Beers list drugs along with possible covariates on four binary complications (readmission, reoperation, mortality and ER visit). Data analysis was conducted using logistic regression:

$$logit(Outcome) = Beer0 + Beer1 + Beer2 + Covariates + \epsilon$$
(2.1)

Controlled covariates include gender ("Male" as reference), race ("White" as reference), age at surgery, BMI, American Society of Anesthesiologists (ASA) score ("1" as reference), Charlson comorbidity index score, length of surgery, anesthesia method and VA center ("General" as reference). Significance level was set as nominal 0.05. Since all covariates are needed for clinical purpose, we did not do model selection.

2.4 Software information

Data analysis was performed with R (Version 3.6.1) for Windows Server 2012 R2 Standard through R studio. Package "ggplot2" was used to generate mean dose count per quarter and distribution of Beers drug dose count; package "Publish" was used to plot confidence intervals for each covariate. Package "qcc" was used to plot statistical control chart.

Chapter 3

Result

3.1 Study population

We identified 12,639 cases from 45 VA medical centers over a five-year study period (2010 to 2014). Most cases were males (93.20%) and white (74.78%). The average age of patients was 65.06 years (SD= 8.49), which is consistent with the VA patients in general. The average BMI was 31.81 with an SD of 5.24 (Table 1), which is higher than the obesity criteria that was set up as 30 [18]. The majority of patients have an ASA score of 3 (73.62%) with severe systemic diseases. Over half of the patients used general anesthesia method (56.93%). The mean Charlson score is 1.01 (SD= 1.56), indicating low number of comorbidities among the patients (Table 1).

3.2 Beers drug usage

3.2.1 General description

Majority of the study subjects (73.4%) used any medication on Beers list, 26.2% using Beers 0 medication (to use with caution), 61.0% using Beers 1 medication (to avoid in all older adults), and 15.6% using Beers 2 medication. Beers 1 was most frequently used on patients with an average dose-count of 2.70 (SD= 3.31), followed by Beers 0 (mean= 0.61, SD= 1.13) and Beers 2 (mean= 0.31, SD= 0.77) (Table 1, Figure 1). In addition, Beers 1 was used more frequently at a large dose (>5) (2339 subjects, 18.51%) than Beers 0 (0 subjects) and Beers 2 (4 subjects, 0.03%).



Figure 1. Log frequency of each Beers Category at each dose count. Log transformation was used for visualization purpose, to make highly skewed distribution less skewed and more comparable.

3.2.2 Dose count trend over years

To examine the trend of using Beers drug over time, we summarize the usage data quarterly.

Over the 5 years, the quarterly mean dose count of Beers 1 is substantially higher than those of Beers 0 and Beers 2 (Figure 2). No obvious trend is observed for Beers 1 and 2 over time; however, increasing trend is observed for Beers 0, especially for 2014. To determine if there is a statistical trend of the quarterly dose-count usage over time for three Beers drug, we used statistical control chart (Figure 3). For Beers 0, there is a clear increasing trend over time. From 2010 quarter 1 to 2011 quarter 1, it's mean dose-counts are all more than three standard deviations lower compared to the overall mean. From 2011 quarter 2 to 2013 quarter 4, almost all quarterly mean dose-counts are smaller than the overall mean although all of them are within the three standard deviation control limits. However, the mean dose-counts for all four 2014 quarters are more than three standard deviations higher than the overall mean.

For Beers 1, there is no clear trend over time. Quarterly mean dose-counts are all within control limit of three standard deviations, and there are no seven or more consecutive points on the same side of that overall mean, which indicates a lack of evidence on random distribution. (Figure 3). For Beers 2, there is a slight decreasing trend over time. Seven consecutive quarterly mean dose-counts are greater than the overall mean dose-count from 2010 quarter 1 to 2011 quarter 3, and 11 consecutive quarterly mean dose-counts are smaller than the overall mean dose-count from 2012 quarter 2 to the end of the study. However, all quarterly dose-counts are within three standard deviations from the overall mean.



Figure 2. Mean quarterly dose count per patient for the three Beers categories: Beers 0 (Medications from the 2015 updated Beers List to be used with caution), Beers 1 (Medications from the 2015 updated Beers List to avoid), and Beers 2 (Medications from the 2015 updated Beers List to avoid in certain disease status).

Variable	Level	N = 12639
Gender	Female	860 (6.80%)
	Male	11779 ($93.20\%)$
Race	white	9451 (74.78%)
	Black	2070 ($16.38\%)$
	Other	1118 (8.85%)
ASA Score	1	49~(~0.39%)
	2	2965 ($23.54\%)$
	3	9275~(~73.62%)
	4	309~(~2.45%)
Anesthesia Method	General	$6930\ (\ 56.93\%)$
	Block	$183\ (\ 1.50\%)$
	Combined	$3452\ (\ 28.36\%)$
	MAC	23~(~0.19%)
	Spinal	1585 ($13.02\%)$
Reoperation within 30 days	Yes	$86\ (\ 0.68\%)$
Reoperation within 90 days	Yes	267 (2.11%)
Reoperation within 365 days	Yes	$380\ (\ 3.01\%)$
Mortality within 30 days	Yes	37~(~0.29%)
Mortality within 90 days	Yes	55~(~0.44%)
Mortality within 365 days	Yes	$159\ (\ 1.26\%)$
Readmission within 30 days	Yes	609~(~4.82%)
Readmission within 90 days	Yes	1131~(~8.95%)
ER visit within 72h	Yes	$220\ (\ 1.74\%)$
ER visit within 7 days	Yes	586 (4.64%)
ER visit within 30 days	Yes	1301 (10.29%)
Age	Mean (SD)	65.06 (8.49)
BMI	Mean (SD)	31.81(5.24)
Charlson comorbidity index score	Mean (SD)	1.01(1.56)
Length of surgery	Mean (SD)	2.13(0.55)
Beers 0 dose count	Mean (SD)	0.61(1.13)
Beers 1 dose count	Mean (SD)	2.70(3.31)
Beers 2 dose count	Mean (SD)	0.31(0.77)

Table 1. Descriptive statistics of interested variables



Figure 3. Statistical control chart of mean quarterly dose count at different time. Upper and lower control limit are set as three standard deviations. Red point represents mean dose count out of limits. Yellow point represents the extra consecutive points (over 7) on the same side of the mean, which suggests lack of evidence for random distribution.

3.3 Length of stay in hospital and complications

On average, people will stay in the hospital for 2.13 days (SD= 0.55) after surgery. Most of them don't have complications after surgery. However, we still have 8.95% of patients who were readmitted within 90 days, 3.01% who were reoperated within 365 days, 1.26% died within 365 days of surgery, and 10.29% went to an emergency room within 30 days after surgery (Table 1).

Since we have 4 types of complications and length of stay, we also examined their correlations. There is a strong correlation among the variables defined by different post-surgery time within each complication type. For example, correlation between mortality within 30 and 90 days is 0.82, and correlation between reoperation within 90 and 365 days is 0.83. Across complications, readmission has a moderate positive association with reoperation and ER visit, which between 0.10 and 0.31. However, no strong correlation was observed among other complications. (Figure 4)



Figure 4. Correlation matrix plot among complications as well as length of stay in hospital. Blue represents positively related and red represents negatively related. Darker color means stronger association and paler color means weaker association.

3.3.1 Relationship between length of stay in hospital and Beers drug dose count

For all three Beers categories, there is a number of patients have long length of stay in the hospital which reaches 40 days, but for most subjects, length of stay is within a week (Figure 5). Although length of stay is close among different dose count, there are significant associations between dose-count and length of stay for all three Beers list drug. The association is negative for Beers 0. For every one-dose increase of Beers 0, length of stay will be 0.06 days or 1.53 hours shorter; However, for Beers 1 and Beers 2, the relationships are positive. They can increase the length of stay by 0.03 and 0.07 days (0.72 hours and 1.68 hours) respectively for every one-dose increase (Table 2).



Figure 5. Boxplot of length of stay in hospital at each dose of Beers medication. A. Length of stay of Beers 0 (Medications from the 2015 updated Beers List to be used with caution); B. Length of stay of Beers 1 (Medications from the 2015 updated Beers List to avoid); C. Length of stay of Beers 2 (Medications from the 2015 updated Beers List to avoid in certain disease status)

	Estimate	Std. Error	t value	$\Pr(> t)$	
Beers 0	-0.063	0.017	-3.682	< 0.001	***
Beers 1	0.025	0.005	5.394	< 0.001	***
Beers 2	0.068	0.020	3.381	< 0.001	***

Table 2. Case length estimates of Beers medication

Analysis was adjusted for gender, race, age, BMI, American Society of Anesthesiologists (ASA), Charlson comorbidity index score, anesthesia method and VA center.

* p-value smaller than 0.05

*** p-value smaller than 0.001

3.3.2 Relationship between four complications and Beers drug

Complications	OR Estimates (95%	CI) for Beers 0	OR Estimates (95% C	I) for Beers 1	OR Estimates (95% C	I) for Beers 2
30 days reoperation	0.99 (0.76-1.29)	_ _	0.97 (0.90-1.04)	-•_	1.26 (0.99-1.61)	
90 days reoperation	0.95 (0.82-1.10)		0.97 (0.93-1.02)	-	1.08 (0.90-1.29)	
365 days reoperation	0.98 (0.86-1.11)	-	0.97 (0.94-1.01)	-	1.05 (0.90-1.23)	-•
30 days mortality	1.01 (0.70-1.47)		1.06 (0.97-1.17)	+•	0.96 (0.64-1.43)	
90 days mortality	1.02 (0.76-1.37)	_	1.05 (0.97-1.13)		1.01 (0.73-1.38)	_ _
365 days mortality	1.03 (0.85-1.24)	_ -	1.02 (0.97-1.07)		0.92 (0.75-1.14)	
30 days readmission	1.01 (0.92-1.11)	+	1.03 (1.00-1.05)	+	1.05 (0.94-1.16)	
90 days readmission	0.97 (0.90-1.05)	-	1.02 (1.00-1.04)	•	1.02 (0.94-1.11)	+
72h ER Visit	1.02 (0.87-1.19)		1.05 (1.01-1.09)	-	1.24 (1.06-1.43)	
7 days ER Visit	0.99 (0.90-1.09)	+	1.04 (1.02-1.07)	+	1.14 (1.03-1.26)	-
30 days ER Visit	1.03 (0.97-1.10)	-	1.04 (1.03-1.06)	+	1.09 (1.01-1.17)	+
		0.6 0.8 1.0 1.2 1.4	1.6	0.8 0.9 1.0 1.1 1.2		0.6 1.0 1.4

dose count

Figure 6. Odds ratio estimates (with 95% confidence interval) for complication outcomes under three Beers categories: Beers 0 (Medications from the 2015 updated Beers List to be used with caution), Beers 1 (Medications from the 2015 updated Beers List to avoid), and Beers 2 (Medications from the 2015 updated Beers List to avoid in certain disease status). Odds ratios are calculated with an increase of every 1 dose count.

Readmission

In the first 30 days after surgery, there are 609 (4.82%) patients came back to the medical centers. When it comes to 90 days, the number reaches 1131 (8.95\%) (Table

1). There is no significant association between the risk of readmission and the dosecount of Beers 0 and Beers 2. However, for Beers 1, a significant increase in risk is observed. The risk of readmission is 1.03 (OR= 1.03, P= 0.0415) times for every one-dose increase within 30 days, and 1.02 (OR= 1.02, P= 0.0409) times within 90 days. (Figure 6, Table 3)

ER visit

Within 72h, 7 days and 30 days, we have 220 (1.74%), 586 (4.64%) and 1301 (10.29%) cases of ER visit respectively. It has a significant association with Beers 1 and Beers 2 (Table 1). For every one-dose increase in Beers 1 medication, the odds of ER visit would be 1.05 (P= 0.01) times within 72h, and 1.04 times (p< 0.01) within 7 days and 30 days. For Beers 2 medication, the odds would be 1.24 (p= 0.005), 1.14 (p= 0.011), 1.09 (p= 0.029) times respectively. Increased dose count of Beers 1 and Beers 2 can lead to a higher risk of ER visit. (Figure 6, Table 3)

Reoperation

There are 86 (0.68%), 267 (2.11%) and 380 (3.00%) patients who were reoperated within 30, 90 and 365 days respectively (Table 1). There is no significant association between the risk of reoperation and Beers 0, Beers 1, and Beers 2, within all three time periods. (Figure 6, Table 3)

Mortality

There are 37 (0.29%) subjects who died within 30 days of the surgery, and the number increase to 55 (0.44%) within 90 days and 159 (1.26%) within 365 days (Table 1). Like reoperation, there is no significant association between Beers use and the risk of mortality within 30, 90 and 365 days (Figure 6, Table 3).

Chapter 4

Discussion

In this study, we analyzed the effect of dose count on readmission, reoperation, mortality, mortality and length of stay. It turned out that Beers 0 has increasing trend over time while Beers 1 and 2 don't. Risk of readmission can be increased by Beers 1, and risk of readmission can be increased by Beers 1 and 2. And all three Beers medications can significantly contribute to the length of stay in hospital, among which, Beers 0 can reduce 1.53 hours and Beers 1 and 2 increase 0.72 hours and 1.68 hours respectively.

The database has been cleaned six times, even though, there are still some problems for data analysis. The original database was in csv format and missing values were marked as NA, which made some variables recognized as character in R. Further data cleaning is still needed before data analysis using the VA database.

Out of clinical consideration, we did not do model selection. All the covariates are clinically relevant. Keeping them in the model are based on the clinician's request.

In the beginning, we plotted the change of four complications rate as dose-count increasing. However, there are lots of high dose-counts ranging from 10 to 160, and for each dose-count, the sample size is small and cannot accurately reflect the actual population rate. To reduce the effect of extreme values, we roughly categorized dosecount of Beers 0, 1 and 2 into three categories: control (0 dose-count), lower dose (0 < dose-count \leq 16) and higher dose (dose-count > 16). Pairwise chi-square analysis was used to analyze the consistency of complication rates among the three categories. However, there is no clinical definition to divide lower and higher dose-count, and every one-dose-count is more meaningful. We decided to treat the dose-count of three Beers list drugs as continuous variables and study on the effect of every one-dose-count increase. To avoid extreme complication rates, we avoided using linear regression of dose count on complication rate. Instead, we decided to use logistic regression since the outcome of four complications are all binary outcomes.

Length of stay and complications are very important indicators of the surgery evaluation. In this paper, we talked about the impact of dose-count on the length of stay and four major complications, but there are also many other factors that may influence the length of stay and complications, such as weekday of surgery and time to physical therapy. Besides, there are also many other small complications which can also be analyzed. At the same time, length of stay may also be an indicator or results of complications. Although they are interesting questions to be discussed, we didn't include them here because we wanted to focus on the effect of Beers list drug dose-count in this paper. We will initiate another paper to discuss the factors that may influence the length of stay, and how the length of stay influence complications.

In this paper, complications were treated as binary outcomes that only includes yes or no. However, the Beers dose-count may also have an influence on the times of complications. In the future study, we will explore the effect of dose-count on times of complications. We can also explore the relationship between exact times of complications and Beers dose-count. Linear regression can be used to do data analysis because complications is a continuous variable. However, because we don't have very large numbers of complication times that greater than 5, and the size of subjects that have multiple complications is small, we can also use another way to do data analysis. Since complication once is more common, and multiple times of complications indicate severer situation. We can divide subjects that had complications into two groups, onetime complication and multiple-time complication. This is still a binary outcome and we can use logistic regression to analyze. However, the sample size will be much smaller since the percentage of patients having complications is very small.

In this paper, we used logistic regression to analyze the effect of Beers dose-count on complications, and the center was treated as a covariate that may influence the outcome. However, since there are 46 VA medical centers, and each center contains lots of subjects, we also used mixed logistic regression model to analyze, treating center as random effect. The result was similar to current logistic regression; thus, we kept the current results. Multivariate multiple regression analysis

In this study, we have multiple complications that have the same covariates; thus, we can also try multivariate multiple regression analysis in the future, including all complications in the model. This method includes the possible correlation among different outcomes. From the correlation plot (Figure 4.), we can see that there is little correlation between most complications, and for this reason, we only used univariate multiple regression analysis. However, there is still some correlation between readmission and ER visit/reoperation, and univariate multiple regression. Current regression analysis will not count such associations. We can try multivariate multiple regression analysis to take into account of the correlations.

In the Beers database, there are 12 random missing values in ER visit. It will not affect the result since the sample size is as large as twelve thousand. However, if we are interested in possible values of those missing data, we can use machine learning methods to predict missing values by dividing available data into training set and testing set, and then missing values can be predicted.

Chapter 5

Appendix

Table 3	n values	of odds	ratio	hotwoon	Boorg	medications	and	complice
Table J.	p-values of	or ouus	Tatio	Detween	Deers	medications	anu	complica-
\mathbf{tions}								

Variable	Time	BEER0	BEER1	BEER2
Reoperation	30 days	0.9470	0.3988	0.0605
	90 days	0.4968	0.2219	0.4032
	365 days	0.7554	0.1515	0.5401
Mortality	30 days	0.9450	0.2010	0.8415
	90 days	0.8863	0.2021	0.9716
	365 days	0.7844	0.4121	0.4647
Readmission	30 days	0.8345	0.0415	0.3963
	90 days	0.4872	0.0409	0.6002
ER Visit	72h	0.8280	0.0159	0.0053
	$7 \mathrm{~days}$	0.8020	0.0013	0.0113
	30 days	0.3185	0.0000	0.0286

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