A Multivariable Prediction Model for 30-day Readmissions for Patients Discharged with Outpatient Intravenous Antibiotic Therapy.

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Abstract

Thirty-day unplanned hospital readmissions contribute to patient morbidity and healthcare costs, and are increasingly scrutinized as a quality measure. Outpatient intravenous antibiotics are used by 250,000 patients per year in the U.S. Awareness of the patient and healthcare associated factors at the time of hospital discharge associated with 30-day readmissions could facilitate targeted approaches to reduce readmissions and improve care. However, factors associated with readmission for patients prescribed intravenous antibiotics at hospital discharge have not been definitively identified to our knowledge. Studies of readmissions for other patient groups have shown conflicting results and predictive models of readmissions have been fair to moderate in their ability to discriminate readmission risk. In this thesis, we describe a new predictive model for patients discharged with outpatient intravenous antibiotic therapy. We conducted a retrospective cohort analysis of 784 patients treated in an outpatient intravenous antibiotic program at a single academic center. We used clinical judgment and statistical criteria to develop a multivariable model of patient characteristics associated with 30-day readmissions. Overall readmission rate was 26%. Our final model included: age by decades (odds ratio 1.09, 95% confidence interval 0.99, 1.21), aminoglycoside use (OR 2.33, 95% CI 1.17, 4.57), presence of resistant organisms (OR 1.57, 95% CI 1.03, 2.36), and number of prior admissions in the past 12 months (OR 1.2, 95% CI 1.09-1.32). Model discrimination was fair (c-statistic 0.61), likely reflecting heterogeneity of the underlying population and post-discharge events. Further studies of outpatient intravenous antibiotics should focus on post-discharge factors that contribute to readmission and are potentially modifiable.

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List of abbreviations

OPAT = Outpatient Intravenous Antibiotic Therapy
HIV-AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome
PI = principal investigator
ID = infectious diseseases

Title

A Multivariable Prediction Model for 30-day Readmissions for Patients Discharged with Outpatient Intravenous Antibiotic Therapy.

Introduction

1.1 Introduction and Rationale for Study

Hospital readmissions, particularly within a 30-day window, are receiving increasing scrutiny from policy makers and payers as high rates of readmission may be markers of lower quality inpatient care or care transitions. Avoiding preventable hospital admissions is important for patient health as well as managing costs of care. Multiple studies have measured factors associated with hospital readmission including patient age (1, 2) male sex (2), length of stay (3, 4), complications during hospitalization (2, 3, 5), comorbidities (2, 3, 5), medical rather than surgical admissions (2), particular diagnoses (6), increased case complexity (7), lower socioeconomic status (8), day of discharge (9), insurance type (10), and prior hospital utilization (2, 3, 5, 10-13). The specific patient factors associated with readmission are inconsistent from study to study, which may be attributable to residual or unmeasured confounding, unmeasured influential covariates, as well as heterogeneity in study populations and types of diseases studied (4).

Outpatient intravenous antibiotic therapy (OPAT) allows patients to receive intravenous treatment at home rather than inpatient settings for the duration of their therapy. Since its inception 30 years ago, OPAT has grown to serve approximately 250,000 persons in the US annually, with healthcare expenditures over $2 billion (14). Multiple studies have demonstrated that OPAT is safe, effective and cost saving to the healthcare system (15-20). Cost-savings for OPAT could improve if rates of unplanned readmissions could be

reduced. OPAT programs coordinate care to avoid adverse events leading to hospital readmissions and other poor outcomes (14). However, to our knowledge a complete understanding of patient and health system factors associated with higher rates of hospital readmissions for patients treated in OPAT programs is currently lacking and there are no developed predictive models to date.

Therefore, we have created a predictive model for 30-day readmissions for patients discharged with outpatient intravenous antibiotic therapy. The multivariable predictive model uses patient and healthcare utilization variables available to clinicians at time of hospital discharge. Identification of easily and reliably obtainable clinical characteristics at the time of discharge that are associated with higher rates of readmission may permit the development of OPAT program interventions with the goal of reducing readmission rates and improving patient outcomes.

1.2 OPAT Background

The rationale for OPAT is simply that OPAT programs provide care that patients prefer, at lower cost compared to inpatient care. In one study of patients receiving OPAT, 96% would chose it again if needed (21), while another study demonstrated that 89% of patients queried prior to discharge would prefer home intravenous antibiotics (as opposed to inpatient) if possible (22). Another study used a priori willingness-to-pay metric as a proxy for personal valuation of inpatient vs. outpatient intravenous antibiotic treatment (23). These researchers found that outpatient treatment was strongly preferred by 87% of

patients surveyed. OPAT programs facilitate patients' ability to have complex care at home, thus promoting a more rapid return to usual activities (i.e. school or work) and improving quality of life (14, 24). Additionally, the provision of this care has been shown to be cost-saving in multiple settings including the United States (22), United Kingdon (21), Italy (25) Ireland (26), Taiwan (27), and Canada (28), focusing on multiple serious conditions such as endocarditis and osteomyelitis that require intravenous treatment for weeks. With an aging population and diminishing funds for healthcare services, demands for OPAT services will likely continue to rise (24).

Composition and Processes of OPAT programs

While having clear quality of life and cost-saving benefits, the home provision of intravenous antibiotics is complicated care being given in a non-medical setting. Patient toxicity, intravenous access problems and infection relapse can undermine the benefits listed previously. One analysis of the processes of discharging a patient with OPAT found 6 main processes and more than 200 sub-processes, any of which could compromise care if imperfectly executed (29). Therefore published guidelines recommend that OPAT programs include communication among medical care providers, teamwork, monitoring and program improvement (30), (14).

The overall composition of an OPAT program can be conceptualized in a framework adapted from the chronic care model described by Bodenheimer et al (31). This OPAT model consists of three interacting domains: patient (patient, support system, comorbidities, and socio-economics), medical providers (physicians, nurses, laboratory technicians,

pharmacists) and a coordination system of patient tracking and iterative program improvement (Figure 1). In addition to functional domains, OPAT can be thought of as having sequential processes, each of which may involve patients, providers and interaction with inpatient and/or outpatient systems. According to published guidelines, OPAT programs should encompass the following processes: patient selection, patient education, Infectious Diseases specialist consultation, discharge planning, communication with outpatient services, tracking of laboratory studies and clinical progress, monitoring for drug toxicity, and periodic quality improvement assessment to facilitate iterative program improvement.

While specifics of patient selection and discharge planning will depend on the resources available at the home medical institution, certain aspects of patient selection are critical to ensure patient success with OPAT. Both United States OPAT guidelines (14) and United Kingdom OPAT guidelines (30), support the careful selection of patients to ensure they are both willing and able to commit to OPAT. For example, patients who lack housing, transportation or telephones must be carefully screened to ensure that OPAT remains the safest option for them. Guidelines also recommend early involvement of Infectious Diseases (ID) specialists to ensure that the infection is under control and that OPAT is both appropriate and necessary to manage the patient's condition. Interventions by infectious diseases specialists during hospital admission to coordinate OPAT care have been found to improve patient outcomes and decrease costs of care (32), (33), (34), (21) by facilitating a switch from intravenous to oral antibiotics in more than one-fourth of patients prior to hospital discharge. While the evidence base for OPAT patient education is lacking, expert

opinions in published guidelines recommend patient education as an important component of OPAT. Patient monitoring is a key component of an OPAT program, and published guidelines suggest which laboratory studies should be monitored, and how often, depending on the specific antibiotic regimen (14). Availability of infusion pharmacists and physicians 24 hours a day to trouble-shoot urgent problems is recommended. Periodic program assessment and quality improvement are also recommended to monitor rates of treatment failure and hospital readmissions.

Materials and Methods

2.1 Study Design

The study is a retrospective cohort with data specifically collected for this study. Index admission is defined as the subject's first episode ever of hospitalization resulting in discharge with OPAT during the study period. We reviewed each subject's admissions prior to the index admission to ensure that they had no prior admissions resulting in discharge with OPAT. We collected index admissions occurring from January 1, 2009 to December 31, 2011 with follow-up through January 31, 2012. The primary outcome for this study is unplanned 30-day readmission, defined as a hospital admission occurring within 30 days of index admission discharge that was not part of a documented plan in the index admission discharge summary. We planned to use the entire cohort in order to capture the range of infectious diseases conditions seen in actual practice. A total cohort n=784 and a theoretical prevalence of a given risk factor of 10% yields 85% power with alpha = 0.05 to detect an absolute readmission rate difference of 15% - i.e. we could detect if subjects with the risk factor have 30% readmission rate while subjects without the risk factor have a 15% readmission rate.

2.2 Participants

The OPAT Research Cohort is a retrospective cohort of 784 patients age 18 and older discharged from Tufts Medical Center with intravenous (IV) antibiotics and followed in the

center's OPAT program (described below) from January 2009 to December 2011. The index admission was defined as the patient's first hospital discharge with IV antibiotics. Patients followed in the OPAT program only on oral antibiotics (n=28), whose entire intravenous antibiotic course was outpatient (n=4), or who used chronic prophylactic intravenous antibiotics spanning multiple admissions (n=2) were excluded from the study (Figure 2). Patients who were readmitted within 30 days for a planned procedure that was documented in the previous discharge summary were also excluded (n = 23, Figure 2). Patients discharged with outpatient intravenous antibiotics who (at the discretion of the primary physician) were not followed in the OPAT program were also not included in this study. These patients constitute <10% of patients at our medical center. This research was approved by the Institutional Review Board of Tufts Medical Center/Tufts University Health Sciences Campus.

2.3 Tufts Medical Center OPAT Program

The Tufts Medical Center OPAT program was developed in 2008 and formally began in 2009 to improve the coordination of care from inpatient to outpatient settings for patients discharged with a requirement for treatment with intravenous antibiotics. The OPAT program was created based on published guidelines advocating a multidisciplinary team approach of inpatient Infectious Diseases (ID) consultation and case management followed by outpatient Infectious Diseases physician clinic visits, home nursing and infusion pharmacists (14). Lean Six Sigma techniques (35) and healthcare process mapping specific to OPAT (29) were utilized to define, create and refine the Tufts Medical Center OPAT program.

Tufts Medical Center OPAT Program Standard Operating Procedures

Patients in the Tufts Medical Center OPAT program are first seen during their hospitalization by ID specialists, who determine medical appropriateness for OPAT. Physicians and case management nurses evaluate patients for potential barriers for home safety. Case management ensures that insurance issues are cleared prior to discharge. An infusion nurse teaches intravenous antibiotic administration techniques to the patient and/or other caregiver while inpatient. Inpatient ID physicians send a template electronic form to the OPAT coordinator who ensures correct antibiotic and laboratory orders and books a follow-up appointment in the Infectious Diseases clinic. If a different ID physician will follow the patient in clinic, the OPAT administrator facilitates communication between inpatient and outpatient physician teams.

After hospital discharge, patients are met at home by a visiting nurse on the day of hospital discharge to review OPAT teaching, treatment plan and problem-solving. Patients are seen in their homes at least once weekly by a visiting nurse who ensures antibiotic compliance, verifies vascular access function and performs phlebotomy for weekly laboratory studies. ID physicians will see patients in the outpatient ID clinic assess clinical response to therapy and manage side effects of medications. Patients will have blood drawn for laboratory studies weekly or more often depending on their clinical situation. Specialty infusion pharmacists oversee the dispensing and delivery of intravenous antibiotics in consultation with Infectious Diseases physicians. Infusion pharmacists and physicians jointly review laboratory results to manage antibiotic drug levels and to detect development antibiotic toxicity and intervene before it becomes clinically evident. The OPAT administrator

coordinates close communication between patients, pharmacists, laboratories, visiting nurses, outpatient clinic staff, and ID physicians.

2.4 Data Collection

Patient data were abstracted by research assistants and the Principal Investigator (P.I.) (GMA) from medical charts into a secure electronic relational database using REDCap (Research Electronic Data Capture) (36). All research assistants were trained and supervised by the P.I. to ensure accuracy of data collection. The following measures were taken to ensure accuracy of data collection by research assistants. All research assistants received training by P.I. (GA), and training modules of chart abstraction were performed until Cohen's kappa score of agreement (37) was minimum 0.8 compared to PI's abstraction. The most challenging abstraction was the prior medical conditions for construction of the Charlson comorbidity index, so this portion of the database was completed by a single research nurse with more than 10 years clinical research experience. Her Cohen's kappa scores of agreement with P.I. were 0.94 for abstraction of prior medical conditions. To avoid temptation for research assistants to guess the correct abstraction categories, multiple questions include answers amounting to "not sure" – all of these responses were subsequently reviewed by P.I. and resolved. All responses "other" for antibiotics, infectious disease diagnoses and vascular access were subsequently reviewed by P.I. (GMA) and resolved.

Data collected included socio-demographic factors (age, race/ethnicity, housing status, social support, insurance status), measures of clinical/healthcare utilization (length of stay,

prior hospital admissions for any cause over past 12 months, laboratory values (admission, discharge, inpatient maximum, inpatient minimum), admission body mass index (BMI), infectious disease diagnoses, type of intravenous access, intensive care unit (ICU) admission, primary service (medicine vs. surgery), past medical history at time of hospital admission and antibiotic(s) at hospital discharge. A random subset of patients (n=414) had intensive data collection to include race, ethnicity, language, BMI, laboratory results and intensive care admission, with the plan to collect these variables for the entire cohort if they met significance level $p<0.2$, which none did. Chart abstractors were not blinded to outcome. All data collection was retrospective with regards to the index admission and readmission.

Variables

A total of 20 candidate variables, selected based on clinical reasoning and review of the literature, were considered in the initial univariate analysis. Age (years), length of stay (days) and number of prior admissions were analyzed as a continuous variable. Intravenous antibiotics were analyzed as categories using a standard classification scheme. Addition of oral antibiotics at discharge was configured as a binary variable. History of any multidrug-resistant organisms ("MDRO") was binary and included any of the following: methicillin-resistant *Staphylococcus aureus,* gram-negative bacteria with expanded-spectrum beta lactamases, or *Clostridium difficile.* Categories of infectious diagnoses were used in keeping with diagnosis categories previously published (20). Diagnoses were not exclusive with the exception of "bacteremia without endocarditis" vs. "endocarditis". A modified Charlson comorbidity index was calculated from prior medical history using standard

methodology described by Quan et al (38). We created a new variable representing immunosuppression (ever/never) which was defined as history of any of following: HIV/AIDS, cancer, transplantation. We initially collected details on type of vascular access then categorized them as either peripherally-inserted vs. central/surgical access. Peripherally inserted lines include peripherally inserted central catheters (PICC) and midlines. Both types of lines are placed in the upper extremity and terminate in the superior vena cava (PICC) or in the mid-axillary region (midline). Central/surgical lines include lines beginning in the neck or chest, or require a surgical procedure for placement (i.e. port-a-cath, dialysis catheter, tunneled line).

The rationale for defining these two groups is that the central/surgical lines may reflect presence of serious medical comorbidities precluding peripheral vascular access placement. We recorded inpatient primary team (surgery, medicine, infectious disease) to measure whether results were affected by primary team and whether therefore these results could be generalized to facilities that utilize a hospitalist method rather than subspecialty primary services. In order to categorize insurance status, we used the following classifications: Medicare, Medicaid, private, uninsured (=free care, self-pay, charity) as published by Jiang et al (39). Commonwealth Care is a relatively new insurance type, held by 15 subjects in this study. We classified Commonwealth care as Medicaid because of this published statement in 2012: "CommCare [Commonwealth Care] is a subsidized market model of coverage for low-income adults. Adults with household income at 300 percent FPL or less may enroll in CommCare if they have no affordable offer of employer coverage and are ineligible for coverage in MassHealth (Medicaid), Medicare, Tricare, or certain other insurance programs. CommCare is offered through the Connector, Massachusetts' flagship

health insurance exchange, but only in CommCare plans can eligible individuals obtain subsidies to offset all or part of the cost of their premiums. CommCare fully subsidizes premiums for adults with income below 150 percent of FPL and partially subsidizes premiums for those with income from 150 to 300 percent FPL, who in general are subject to Massachusetts' individual mandate (40)."

To improve overall project feasibility, we had an intensive data collection process for a randomly chosen subset of 414 subjects (see Figure 1, research subject cohort flow) involving race/ethnicity, language, laboratory values, body mass index (BMI) and intensive care unit admission. Results from t-test comparing readmitted vs. non-readmitted groups at the $p<0.05$ level determined whether these covariates would be collected for the entire cohort. Racial categories were based on Center for Disease Control (CDC) categories (41) (American Indian/Alaskan native, Asian/Pacific Islander, Black/African American, White, Other, Missing. Hispanic ethnicity was collected as a binary variable separately from race in accordance with accepted CDC practice (41). Primary language was collected as Chinese, English, Spanish, Other, Missing. We recorded BMI if it was measured at time of hospital admission. The following laboratory values were recorded for each patient as continuous variables: albumin as proxy for nutritional status, alanine aminotransferase (ALT) as proxy for liver inflammation, race-appropriate estimated glomerular filtration rate (GFR) as proxy for renal function (42), white blood cell count, absolute neutrophil count and Clostridium difficile stool toxin test results. BMI (kg/m^2) and laboratory studies were recorded as continuous variables. WBC and ANC are measured as number of cells $x10^9/L$, ALT measured as units/L, eGFR measured as ml/min/1.73 m^2, albumin measured as g/L. In order to collect proxies of disease severity which could potentially affect readmissions, we

collected history of intensive care unit (ICU) admission during index admission as a binary variable.

Sensitivity Analysis

To address the threat of outcome misclassification bias due to loss to follow-up (i.e. patients potentially readmitted to a hospital other than Tufts Medical Center being classified as non-readmissions), we reviewed subsequent medical services for all subjects who were not readmitted within 30 days (n=575), and found that 78 (14%) subjects had no additional services at Tufts Medical Center following hospital discharge. We performed two sensitivity analyses to address potential misclassification in the event that these subjects were actually readmitted elsewhere. The first sensitivity analysis removed all 78 subjects from the data set, and the second reclassified them as readmissions.

2.5 Statistical Analyses

Descriptive characteristics were summarized using means and standard deviations for normally distributed variables and using medians and interquartile ranges for skewed data. Clinical and demographic characteristics were compared between readmitted and non-readmitted patients using the Student's t, Wilcoxon rank-sum, Pearson χ^2 and Fisher exact tests, as appropriate. Odds ratios and 95% confidence intervals were calculated using logistic regression. $P<0.2$ was considered significant for candidacy of a variable in the multivariable predictive model. Age was included in all multivariable models by *a priori* decision as advancing age has been found to be significantly associated with readmission (1, 2). We then utilized backwards selection using Akaike's information criterion (AIC) as

opposed to Bayesian information criterion (BIC) (43). AIC was chosen *a priori* as the underlying method as our goal was to find a best-fit model for the data, not the only correct model. Model selection was followed by analysis of leverage and influence points, variable collinearity, and regularized regression using the Lasso (44). The final model's performance was characterized by receiver operator curve analysis (45), calibration curves and Hosmer-Lemeshow goodness-of-fit (46). We used the following model diagnostics: Cook's distance to evaluate influence points, Lasso as correction for model overestimation. We examined age and readmissions for non-linear relationships. Statistical analyses used R Statistical Program version 2.13.1 (updated July 22, 2011, copyright R Foundation, from http://www.r-project.org). All *p*-values are 2-sided.

Results

3.1 Main Results

Study inclusion and exclusion details are presented in Figure 2. Demographic and clinical characteristics of the cohort are summarized in Table 1a, antibiotics and infectious diseases diagnoses in Table 1b. The mean age of the study population was 58 years, with readmitted patients being slightly older. 57% percent of patients were male. Prior admission was significantly more common among readmitted patients ($p<0.001$) as was prevalence of MDRO (21% vs. 15%, $p= 0.037$). Immunosuppression had higher prevalence among readmitted patients (31% vs. 21%), but this was not statistically significant ($p=0.1$). Readmitted patients appeared somewhat less likely to be living with another adult 63% (130/207) than non re-admitted admitted patients, 69% (397/575), $p=0.06$). For the intensive data collection subset (n=414), we found race, ethnicity, English language as first language, and intensive care unit admission to be similar among non-readmitted and readmitted subjects (see page 22, bottom of Table 1a).

As shown in Table 1, five infectious disease diagnoses (cellulitis, endocarditis, pyelonephritis/urinary tract infections, pneumonia, and bacteremia) met criteria to be considered as candidates for the multivariable model. Patients who were prescribed aminoglycosides were associated with a two-fold higher odds of readmission ($p=0.04$) compared to patients who did not use this drug class. Anti-*Staphylococcal* penicillin class antibiotics (oxacillin, dicloxacillin, nafcillin) were associated with a 33% reduced odds for readmission compared to those who did not use this drug class, though this difference was

not statistically significant. Vancomycin was not associated with increased readmission risk (crude odds ratio 1.13, p=0.48).

Multivariable Results

We applied statistical criteria and clinical judgment to develop a final multivariable model that included age, prior admissions, MDRO and aminoglycoside use (Table 2). C-statistic is 0.611 for final model. Calibration curves (Figure 3) indicate that patients in the highest quintile of predicted readmission risk have more than double the readmission odds compared to the lowest quintile readmission risk (lowest = observed 17.8%, predicted 18.3%, and highest = observed 43.6%, predicted 40.0%). Hosmer-Lemeshow test result for goodness-of-fit was $\chi^2 = 5.5$ (p=0.7).

3.2 Sensitivity Analyses

Compared to the remaining cohort, the 78 patients who were potentially lost to follow-up after hospital discharge had fewer prior admissions in the preceding 12 months (0.5 vs. 1.1, p<0.01) and were more likely to get post-inpatient antibiotics in a rehabilitation facility as opposed to home (58% vs. 46%, p=0.05). They were not significantly different from the remaining cohort in terms of age, sex, use of aminoglycosides, and length of stay, as shown in Table 3. Sensitivity analyses either leaving these patients out of the analysis or classifying all as readmissions did not meaningfully change the final model odds ratios, as shown in Table 2.

3.3 Model Diagnostics

Using Cook's distance, full model was examined for influence points. 4 subjects were found with leverage >0.06 (Figure 4). The initial full model included the following readmission predictors: age + bacteremia + cellulitis + urinary tract infections + pneumonia + endocarditis + mdro + inpatient service + number of prior admissions + anti-Staphylococcal penicillins (e.g. oxacillin) + aminoglycosides. These 4 high-influence subjects were removed from the dataset and Cook's distance was measured comparing the results with and without the influence points (Figure 5). The full multivariable model was re-analyzed after removing these four outliers using backwards selection with AIC. Using this selection scheme, bacteremia was no longer found to contribute significant information to the model, and the remaining model variables were age, prior admission, cellulitis, aminoglycosides and MDRO. In order to ensure the model was not driven by subjects with overly high influence, these four subjects remained out of the final model.

To account for potential overestimation of regression coefficients, we used the Lasso (least absolute shrinkage and selection operator). Using regularized logistic regression, squared error of coefficients was minimized at 3 variables: prior admissions, aminoglycosides, and MDRO. Lambda (optimal model complexity) was estimated using 10-fold cross-validation. Using a less restrictive lambda 0.026 optimized the model with six variables: age, bacteremia, pneumonia, aminoglycoside, prior admission, and MDRO.

Given that bacteremia, cellulitis and pneumonia were not consistently part of final models described above, they were eliminated from the final model on both statistical and clinical grounds. Therefore the final model variables are: age, prior admission, MDRO and

aminoglycoside use. Collinearity of these final model variables was measured using the variance inflation factor (vif). Vif was < 1.02 for each variable, with vif > 5 indicating collinearity. Thus we concluded that these variables were not collinear.

Testing for Linearity of Age and Prior Admissions

Age was assessed for nonlinear relationships with readmission risk using a spline function with 4 knots. This demonstrated a monotonic relationship of age with increased readmission risk, likely modeling a monotonic relationship with some variability (Figure 6). Given the inflection point at approximately age 50 year, we tested for higher order interactions of age with readmission and examined the effect on the multivariable model of adding a variable of age to second, third and fourth power respectively. None of these higher-order age variables had a statistically significant association with 30-day readmissions. Also, the estimated betas for the non-age-related variables in the multivariable model (prior admission, MDRO and aminoglycosides) changed by 1% or less when adding higher-order age variables. (Table 4). T-test of coefficients showed no significant difference between these iterations of the model (p=0.287). Akaike information criterion (AIC) was maintained between 886 and 888, showing no additional model improvement with adding higher power age variables.

We also assessed whether prior admissions could have a nonlinear relationship with readmission risk. Spline function of prior readmissions demonstrated linear relationship (see Figure 7). When adding prior admission as a quadratic term, model was not significantly difference by t-test of coefficients (p=0.3129)

Discussion

Among patients followed within our OPAT program, the overall rate of 30 day readmission was high (26%) but similar to those in other published OPAT cohorts (47-49). Patients who were readmitted were similar in most respects to patients not readmitted. However, they were more likely to be older, have a prior admission within the last year, have an infection with a multidrug resistant organism, or to have been receiving an aminoglycoside rather than another antibiotic. Using these easily obtainable variables permitted stratification of the OPAT population into risk quintiles, such that the highest risk quintile had a readmission risk that was 2-fold higher than the lowest. C-statistic for the model is 0.61, with modest discrimination ability. While this gives some discrimination at the extremes, the discrimination ability for the mid-range risk is not as strong, where guidance is needed more. The Hosmer-Lemeshow test statistic p=0.7 implies that the observed and expected values are not significantly different and the model fits the data acceptably well.

Similar to other studies (2, 3, 5, 10-13), prior admissions had the strongest association with readmissions. We did not find vancomycin associated with readmissions. Our model found that use of aminoglycoside was associated with a doubling of risk of 30-day readmission. Given the nephrotoxicity of aminoglycosides, and their reservation for use in serious conditions, this increase in risk seems clinically plausible, though the relationship

may not be causal. Similarly, MDRO may be a marker for difficult-to-treat organisms or for overall disease severity.

Unlike other studies of hospital readmissions (8, 10), we did not find any demographic characteristics were associated with readmission risk, aside from a borderline association of readmission with higher age. It is possible that the additional support – both inpatient and outpatient – of patient teaching and care coordination in OPAT programs help address unmeasured healthcare disparities that usually cause readmission rates to be higher among minority or lower socio-economic populations. Overall model discrimination was in a range usually considered modest (C-statistic 0.611), but this performance is in alignment with many other hospital readmission scores calculated from substantially larger cohorts (reviewed by Kansagara et al, 2011 (50)). Overall, all the subjects in this study are at high risk for readmission. Therefore the model may serve to identify higher risk patients who might benefit from additional home resources to avoid readmission as opposed to identifying low-risk patients who need less intervention. Further prospective studies are needed to measure whether identification and intervention for high-risk patients improves outcomes in the OPAT setting.

Some authors have raised concern regarding the use of 30-day readmission as a quality metric. Vaduganathan (51) argued that the 30-day time frame is not biologically relevant and this focus may have unexpected adverse consequences such as hospitals that improve post-discharge mortality being penalized for increased readmissions, due to removal of the competing risk. Additionally, others have raised concerns about the use of a quality metric

that is influenced by so many factors outside the inpatient team's control, including noncompliance, trauma, and worsening of other unrelated comorbidities (52). These concerns notwithstanding, the use of 30-day readmission rates as an important quality metric creates intense interest on identifying especially high risk patients. Yet the influence of post-discharge factors that are difficult to control and measure may make readmission prediction highly challenging.

One limitation is that we did not analyze subsequent readmissions, so this model may only be applicable for the first readmission. Another limitation is the possibility of misclassification bias for subjects who do not return to the study institution. However, we found in sensitivity analyses that removing these subjects from the data set or reclassifying them as readmissions did not meaningfully influence our results. The heterogeneity of conditions treated may have contributed to the low discrimination of the model, with the potential for different predictors of readmission among the subpopulations. Our prediction model strictly utilized medical record data that was collected at the time that care was being provided, thus we minimized the risk of recall bias in a retrospective cohort study.

Study strengths include capture of planned versus unplanned nature of the readmission, which is not always accomplished in readmission studies (50). We studied a wide range of patient demographic and clinical variables and our study was powered to detect changes in readmission rates with relatively low prevalence risk factors on the order of 10%. The breadth of conditions treated may promote generalizability of this model among hospitalized patients and ensures that this model is relevant to actual clinical practice.

Since subjects were referred to the OPAT program by their inpatient infectious diseases consultants, we presume that data on infectious diagnoses and antibiotic treatments were correctly documented in the medical record. Diagnoses and treatment were abstracted from individual patient medical records as opposed to billing or other administrative data, further increasing the accuracy of exposure and covariate classification.

Future directions for this research could include additional medical factors that could be related to readmissions. Additional medical history variables that could be collected retrospectively include day of discharge (i.e. weekend vs. weekday) and antibiotic switches prior to discharge. Rationale for studying antibiotic switches is that if a patient's first dose of the OPAT drug is on day of discharge, clinically meaningful side effects will not manifest until the patient is an outpatient. Would inpatient antibiotic switches be associated with higher risk of readmissions? This study could be quite complicated, as some of the switches may be from less tolerated to better tolerated drugs, while other switches could be the reverse.

Additional variables that could be collected prospectively that could add some insight into previously unmeasured OPAT processes could include: confidence of OPAT success in the opinion of the infectious diseases consultant; confidence of OPAT success in the opinion of the patient; formal assessment of medical literacy of the patient – low medical literacy has been shown in general medicine wards to be associated with readmission risk. Does the OPAT teaching overcome patients' baseline medical literacy gaps?

In summary, readmission was a common issue in our OPAT cohort. We created a predictive model for hospital readmissions for OPAT patients that relies on 4 easily obtainable clinical variables: age, prior admissions in past 12 months, aminoglycoside use and history of resistant organisms. In keeping with many other researchers' experiences, model discrimination was modest by conventional standards. Not surprisingly, the strongest predictor of readmission was the number of prior hospitalizations. Future work should examine the influence of potentially modifiable post-hospital OPAT care activities and characteristics of different OPAT programs on readmission rates and clinical cures, and consider additional variables such as day of discharge and inpatient antibiotic changes that may also increase risks of readmissions.

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Figures

Figure 1. Conceptual Model of OPAT.

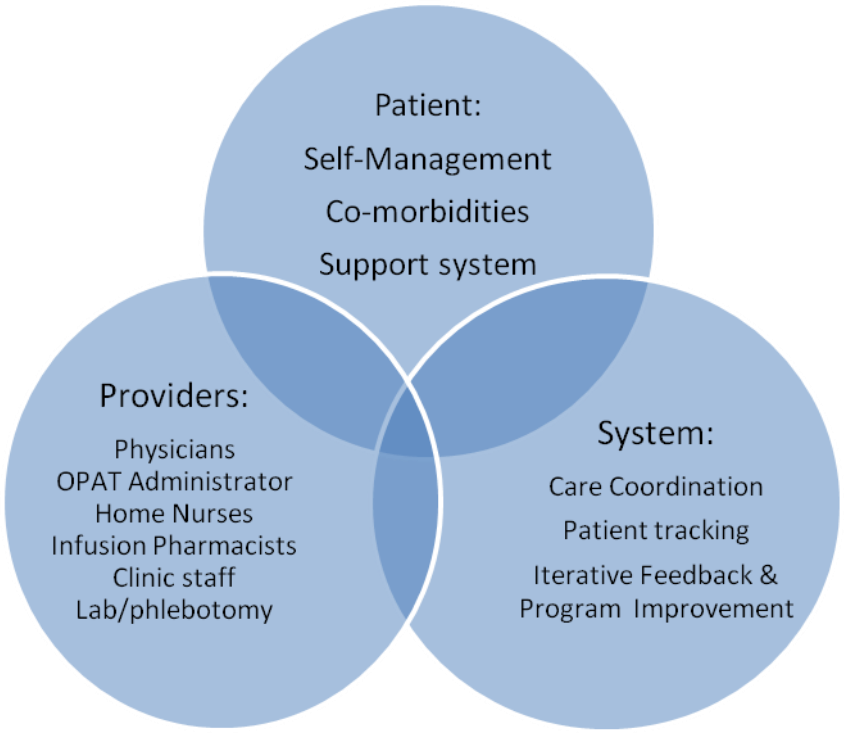

Figure 2. OPAT Research Cohort Subject Flow Diagram

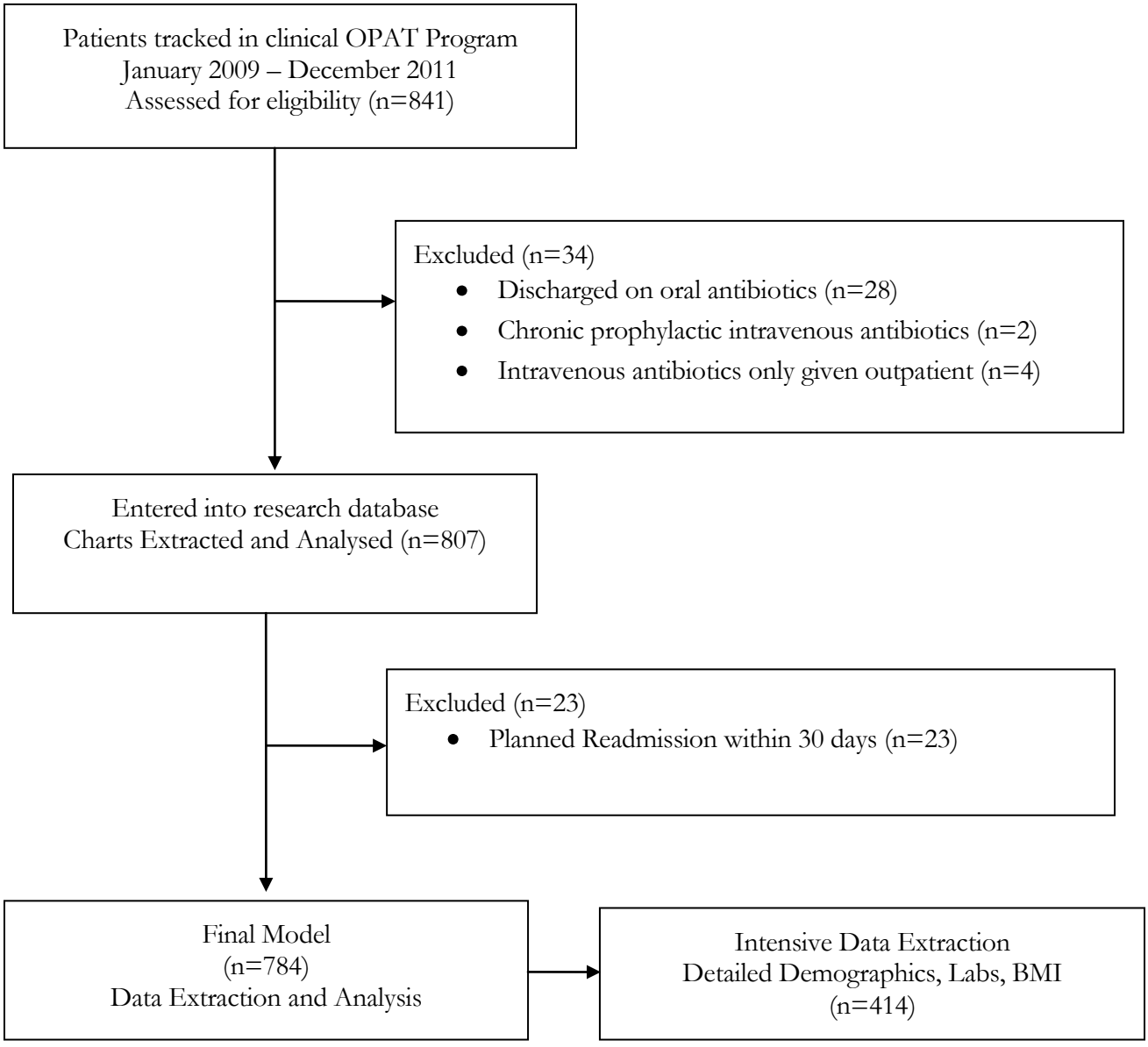

Figure 3. Calibration curve for multivariable model

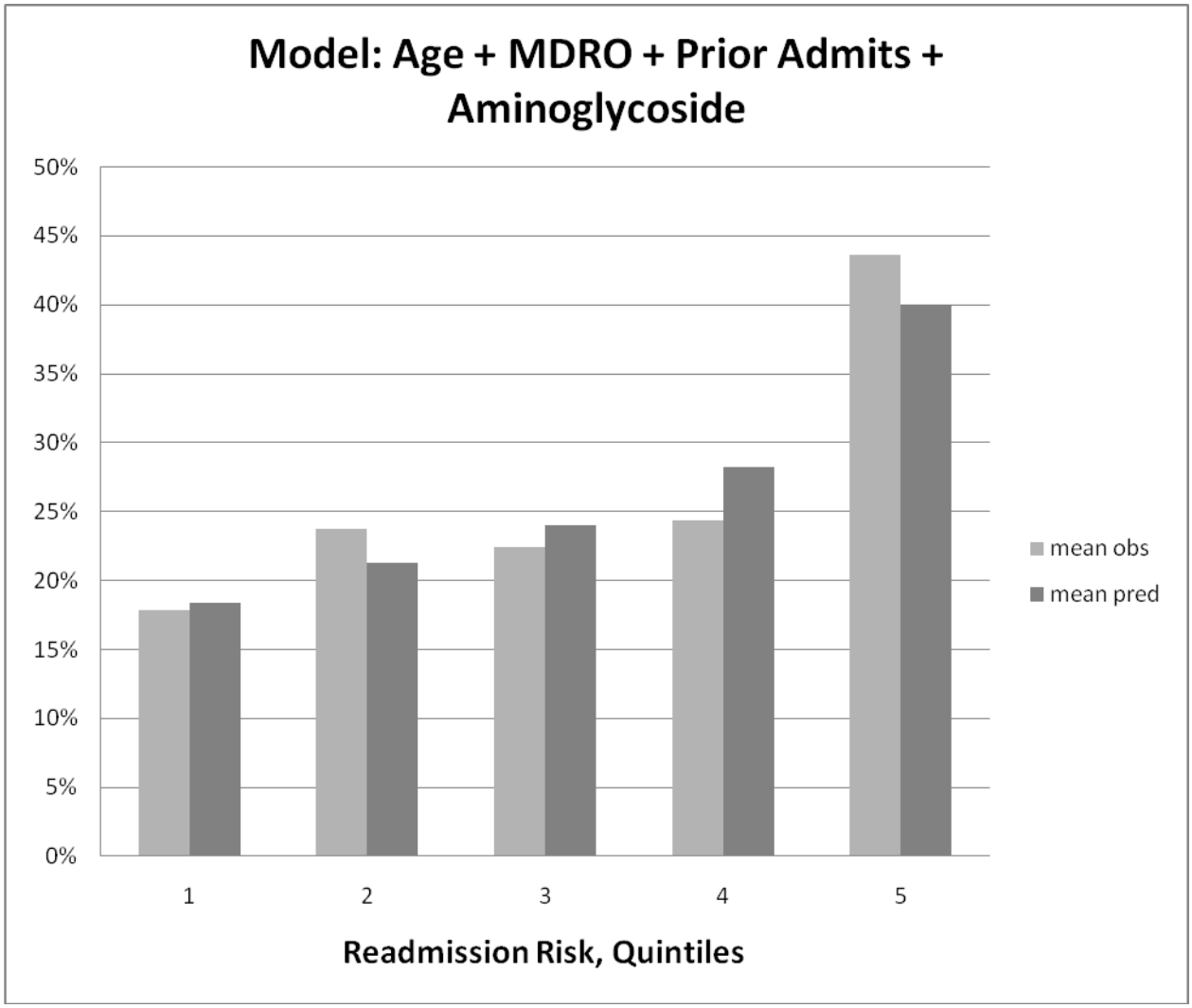

Figure 4. Influence points

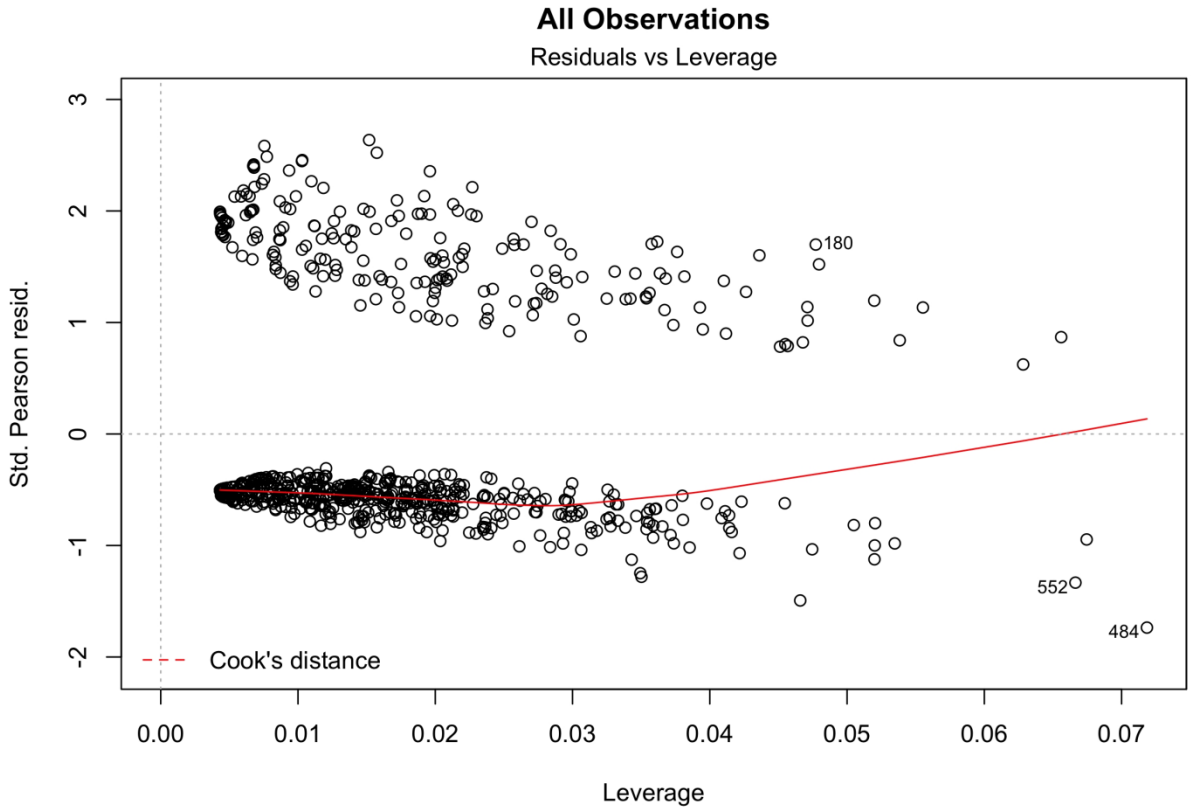

Figure 4 illustrates that four subjects have a high influence on the performance of the initial full model as measured by Cook's distance.

Initial full model: readmission predictors: age + bacteremia + cellulitis + urinary tract infections + pneumonia + endocarditis + mdro + inpatient service + number of prior admissions + anti-Staphylococcal penicillins (e.g. oxacillin) + aminoglycosides.

Figure 5. Cook's distance with and without influence points

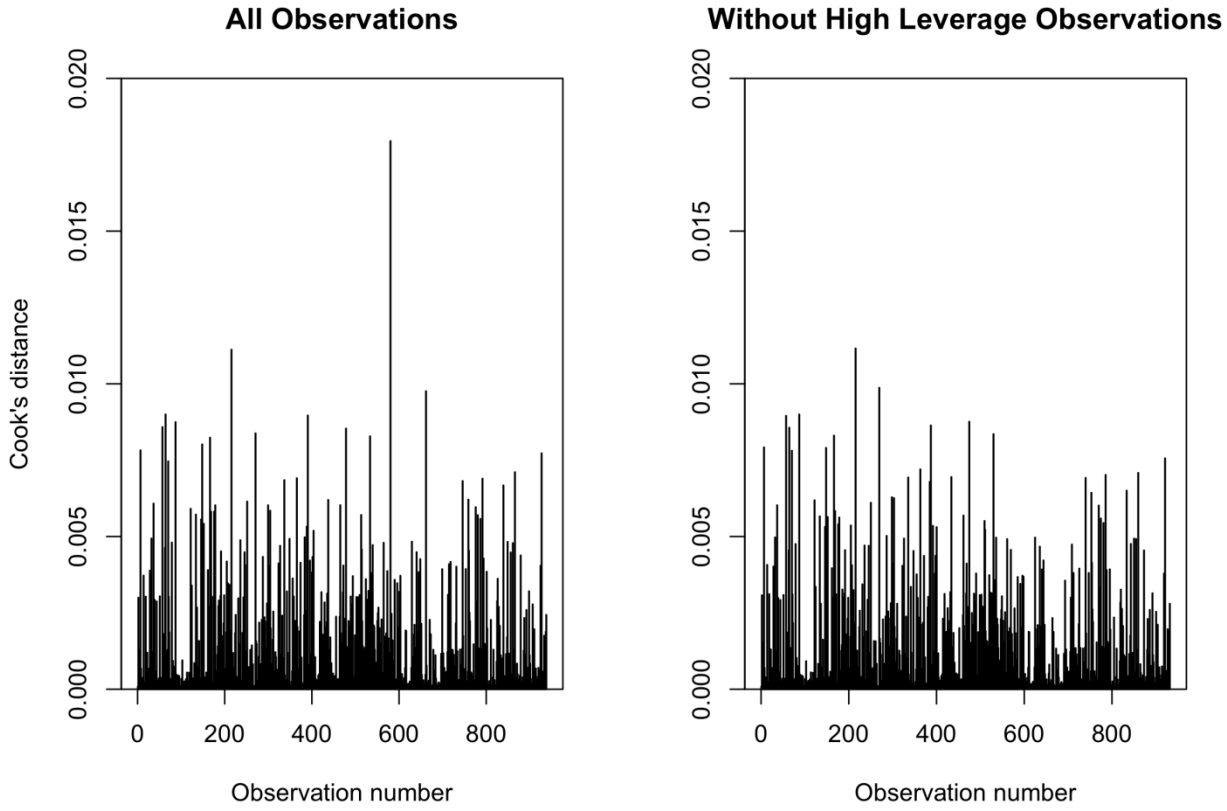

Figure 5, left graph, illustrates Cook's distance for the initial full model with all subjects, while Figure 5, right graph, illustrates Cook's distance for the initial full model with 4 high-leverage subjects removed.

Initial full model: readmission predictors: age + bacteremia + cellulitis + urinary tract infections + pneumonia + endocarditis + mdro + inpatient service + number of prior admissions + anti-Staphylococcal penicillins (e.g. oxacillin) + aminoglycosides.

Figure 6. Age Splines

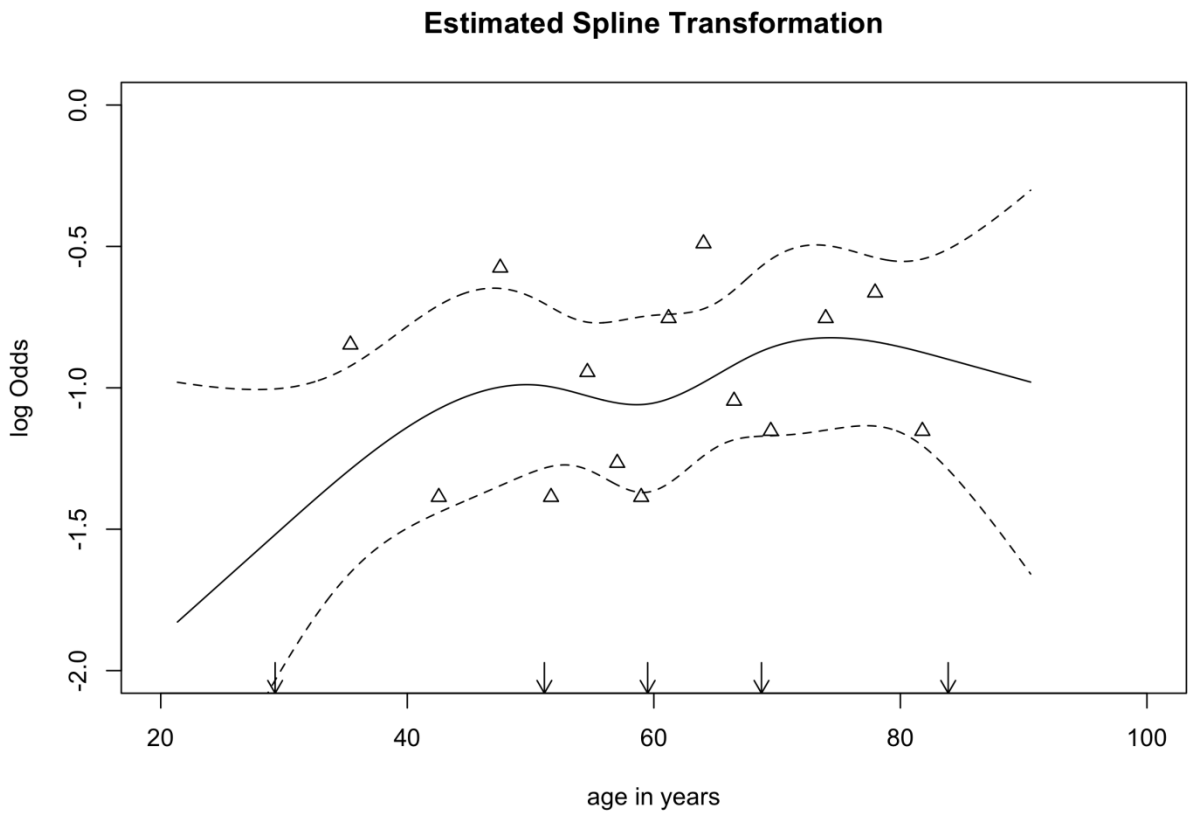

Figure 6 demonstrates a monotonic relationship with age and readmission risk, with inflection points likely related to intrinsic variability. As shown in Table 4, adding higher-power age variables did not improve the model performance.

Figure 7. Estimated prior admission splines.

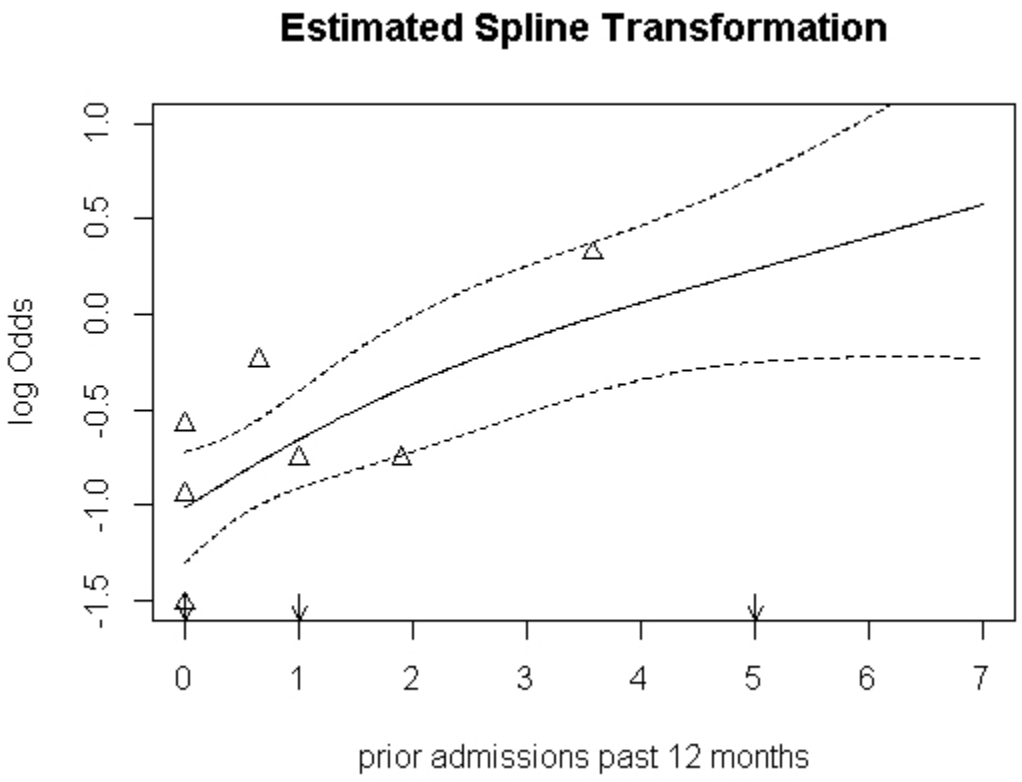

Figure 7 demonstrates a monotonic relationship with age and readmission risk.

Tables

Table 1a. Demographic and clinical characteristics of study cohort (N=784)

Characteristic	**Total study n = 784**		**Readmitted n = 207**		**Not Readmitted n = 575**		**p value**
Demographics							
Age, years: mean (SD)	58	(16)	61	(15)	58	(16)	0.06
Sex: n,% Male	446	57%	123	59%	326	57%	0.50
Insurance: n, % Medicare Medicaid Private Self-pay	 338 102 337 5	 43% 13% 43% 1%	 93 25 89 0	 45% 12% 43% 0%	 245 77 248 5	 43% 13% 43% 1%	0.71
Support Status: n, % Lives alone, no supports Lives alone, has friend/family support Lives with at least one adult Missing support status	 53 139 527 63	 7% 18% 67% 8%	 12 40 130 25	 6% 19% 63% 12%	 41 99 397 38	 7% 17% 69% 7%	0.07
Comorbidities Charlson comorbidity index: median (IQ range)	 2	 (0, 3)	 2	 (1,3)	 2	 (0, 3)	0.34
Diabetes mellitus without complications Diabetes mellitus with complications No Diabetes	140 95 547	18% 12% 70%	40 31 136	19% 15% 66%	100 64 411	17% 11% 71%	0.23
Renal disease, no dialysis Renal disease, dialysis No Renal disease	130 59 593	17% 8% 76%	38 19 150	18% 9% 72%	92 40 443	16% 7% 77%	0.36

Table 1a continued. Demographic and clinical characteristics of study cohort (N=784)

Characteristic	**Total study n = 784**		**Readmitted n = 207**		**Not Readmitted n = 575**		**p value**
History of Multidrug Resistant Organism	130	17%	44	21%	86	15%	0.04
Immunocompromised	211	27%	52	25%	180	31%	0.10
Healthcare Utilization							
Oral antibiotic yes	176	23%	50	24%	126	22%	0.51
Oral antibiotic no	602	77%	155	75%	447	78%	
missing oral antibiotics, n	4	1%	2	1%	2	0%	
Length of stay, days: median (IQ range)	6	(4,10)	7	(4, 10)	6	(4,10)	0.68
Quintiles (based on equivalent density)							0.75
1-4	227		53		174		
5	95		24		71		
6-7	149		41		108		
8-12	170		49		121		
13-102	140		39		101		
Number of Prior admissions in past 12 months: mean, (std)	1.1	(1.8)	1.5	(2.2)	0.9	(1.5)	<0.001
Peripheral access (PICC, Midline)	679	87%	181	88%	486	85%	0.257
Inpatient Service							
Medicine	330	42%	97	47%	233	41%	0.160
Surgery	288	37%	75	36%	213	37%	
Infectious Disease Ward	164	21%	35	17%	129	22%	

Table 1a continued. Demographic and clinical characteristics of study cohort (N=784)

	Subset study n = 413		**Readmitted n = 140**		**Not Readmitted n = 273**		**p value**
Race, Ethnicity, Language: n, %							
Caucasian	314	76%	108	77%	201	74%	0.40
Hispanic	14	3%	4	3%	14	5%	0.20
English first language	359	87%	124	89%	236	86%	0.54
Intensive care unit admission	80	19%	30	21%	50	18%	0.510

Table 1b. Antimicrobial and infectious disease diagnoses of study cohort

Class description **Specific antimicrobials**	**Total n=784 n, %**		**Readmitted n=207 n, %**		**Not readmitted n=575 n, %**			**% (ratio) admitted if Risk Factor present**	**% (ratio) admitted if Risk Factor not present**	**Odds Ratio**
Cephalosporin cephalexin, cefuroxime, cefazolin, ceftriaxone, cefoxitin, cefepime, ceftaroline, ceftazidine	199	25 %	53	26%	146	25%	0.95	27% (53/199)	26% (154/583)	1.01
Carbapenems aztreonam, ertapenem, imipenem, meropenem	149	19 %	42	20%	107	19%	0.60	28% (42/149)	26% (165/633)	1.11
anti-*Staphylococcal* beta-lactams dicloxacillin, nafcillin, oxacillin	104	13 %	21	10%	83	14%	0.12	20% (21/104)	27% (186/678)	0.67
Fluoro-quinolones ciprofloxacin, levofloxacin, moxifloxacin	63	8%	21	10%	42	7%	0.20	33% (21/63)	26% (186/719)	1.43
Daptomycin	41	5%	11	5%	30	5%	0.96	27% (11/41)	26% (196/741)	1.02
Aminoglycoside amikacin, gentamicin, tobramicin, inhaled tobramicin	39	5%	16	8%	23	4%	0.03	41% (16/39)	26% (191/743)	2.01

Table 1b continued. Antimicrobial and infectious disease diagnoses of study cohort

Class description **Specific antimicrobials**	**Total n=784 n, %**		**Readmitted n=207 n, %**		**Not readmitted n=575 n, %**			**% (ratio) admitted if Risk Factor present**	**% (ratio) admitted if Risk Factor not present**	**Odds Ratio**
Synthetic nucleoside analog antivirals: acylovir, famciclovir, ganciclovir, valacyclovir, vanganciclovir	37	5%	9	4%	28	5%	0.76	24% (9/37)	27% (198/745)	0.89
anti-*Pseudomonal* beta-lactams piperacillin-tazobactam	31	4%	7	3%	24	4%	0.62	23% (7/31)	27% (200/751)	0.80
Azole antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	29	4%	11	5%	18	3%	0.15	38% (11/29)	26% (196/753)	1.74
Metronizadole	28	4%	9	4%	19	3%	0.49	32% (9/28)	26% (198/754)	1.33
Infectious Disease Diagnosis	**Total n=784 n,%**		**Readmit n=207 n,%**		**Not readmitted n=575 n,%**			**% (ratio) admitted if RF present**	**% (ratio) admitted if RF not present**	**Odds Ratio**
Bacteremia	190	24 %	61	29%	129	22%	0.04	32% (61/190)	25% (146/592)	1.44
Osteomyelitis or Septic Arthritis of Native Joint	159	20 %	39	19%	120	21%	0.53	25% (39/159)	27% (168/623)	0.88

Pyelonephritis or Urinary Tract Infection	103	13 %	34	16%	69	12%	0.11	33% (34/103)	25% (173/679)	1.44

Table 1b continued. Antimicrobial and infectious disease diagnoses of study cohort

Infectious Disease Diagnosis	**Total n=784 n,%**		**Readmit n=207 n,%**		**Not readmitted n=575 n,%**		p	**% (ratio) admitted if RF present**	**% (ratio) admitted if RF not present**	**Odds Ratio**
Intra-abdominal	86	11%	22	11%	64	11%	0.84	26% (22/86)	27% (185/696)	0.95
Endocarditis	78	10%	26	13%	52	9%	0.15	33% (26/78)	26% (181/704)	1.44
Pneumonia	74	9%	27	13%	47	8%	0.04	36% (27/74)	25% (180/708)	1.68
Cellulitis	61	8%	12	6%	49	9%	0.21	20% (12/61)	27% (195/721)	0.66
Prosthetic Joint Infection	59	8%	14	7%	45	8%	0.62	24% (14/59)	27% (193/723)	0.85
Sepsis	38	5%	10	5%	28	5%	0.98	26% (10/38)	26% (197/744)	0.99
Central nervous system	36	5%	7	3%	29	5%	0.33	19% (7/36)	27% (200/746)	0.66
Cardio/ Vascular Device	34	4%	11	5%	23	4%	0.43	32% (11/34)	26% (196/748)	0.48
Epidural abscess	25	3%	7	3%	18	3%	0.86	28% (7/25)	26% (200/757)	1.08
Diabetic Foot Infection	20	3%	3	1%	17	3%	0.24	15% (3/20)	27% (204/762)	0.48
Cytomegalo-virus infection	20	3%	3	1%	17	3%	0.24	15% (3/20)	27% (204/762)	0.48

Antibiotics used in fewer than 20 subjects are not included in table (n): penicillin (19), echinocandins (19), trimethoprim-sulfamethoxizole (18), amoxicillin/ampicillin group (16), oral vancomycin (15), macrolides (14), linezolid (11), oral rifamycins (11), tigecycline (6), tetracycline group (4), amphotericins (1), atovaquone (1), macrodantin (1), and nonabsorbed oral antifungals (1).

Infectious diseases diagnoses occurring in fewer than 20 subjects are not in table (n): septic shock (12), oto-laryngeal (9), invasive fungal infection (9), diarrhea (5), myositis (3), babesiosis (1), Whipple's disease (1), source unknown (1).

Table 2. Final Model Adjusted Odds Ratios and Sensitivity Analyses

Multivariable Model					Sensitivity analysis 1		Sensitivity analysis 2	
	Odds Ratio	95% confidence interval		p	Odds Ratio	% change from original	Odds Ratio	% change from original
age, per 10 years	1.09	0.99	1.21	0.10	1.10	0.9%	1.10	0.9%
aminoglycoside use	2.33	1.17	4.57	0.01	2.24	-4.1%	1.95	-16.5%
MDRO	1.57	1.03	2.36	0.03	1.46	-6.8%	1.36	-13.2%
prior admissions, n	1.20	1.09	1.32	<0.001	1.17	-2.4%	1.09	-9.1%

Sensitivity analysis 1: eliminate 78 subjects from model who never had follow-up at study institution

Sensitivity analysis 2: Change outcome of 78 subjects to "yes readmission" who never had follow-up at study institution (in case they were readmitted elsewhere)

Table 3. Demographics of lost to follow-up subjects

	lost to follow-up, n=78	not lost to follow-up, n= 704	p value
age, mean years,	60	59	0.66
% male	63%	57%	0.31
% history MDRO	15%	17%	0.76
Mean Number of prior admissions in past 12 months	0.53	1.13	<0.01
Median Length of stay, days	10	9	0.21
% Received antibiotics at rehabilitation facility	58%	46%	0.05
% Received Aminoglycosides	5%	5%	0.95

Table 4. Higher order variables for age

	Beta: age linear	p	Beta: age^2	% change from age linear model	p	Beta: age^2 + age^3	% change from age linear model	p	Beta: age^2 + age^3 + age^4	% change from age linear model	p
(Intercept)	-1.91	0.00	-2.72	43%	<0.01	-3.98	109%	0.08	-3.25	71%	0.55
age per 10 years	0.09	0.08	0.40	334%	0.20	1.17	1179%	0.37	0.55	506%	0.90
MDRO	0.44	0.04	0.44	0%	0.04	0.44	1%	0.04	0.45	1%	0.04
Number of Prior Admissions, past 12 months	0.17	0.00	0.17	0%	<0.001	0.17	1%	<0.001	0.17	1%	<0.001
Aminoglyco-side	0.75	0.03	0.74	0%	0.03	0.75	1%	0.03	0.75	1%	0.03
age^2 per 10 years	n/a		-0.03	n/a	0.32	-0.17	549%	0.47	0.01	-136%	0.99
age^3 per 10 years	n/a					0.01	n/a	0.54	-0.01	-262%	0.93
age^4 per 10 years	n/a								0.00	n/a	0.88
AIC	886		886			888			888		

MDRO = multidrug resistant organisms
AIC = Akaike information criterion

Table 4 demonstrates that adding age squared, cubed or to a fourth power does not change the estimated betas for the other model variables by more than 1%. Large changes of lower-order age variables are expected when adding higher-order variables because of adding unnecessary degrees of freedom. AIC is essentially unchanged with adding higher power age variables, demonstrating no improvement in the model with adding these additional variables. Thus we conclude that keeping age as a linear variable is reasonable.