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Using Machine Learning to Examine Medication Adherence Thresholds and Risk of Hospitalization

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Abstract

Background—Quality improvement efforts are frequently tied to patients achieving ≥80% medication adherence. However, there is little empirical evidence that this threshold optimally predicts important health outcomes.

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Objective—To apply machine learning to examine how adherence to oral hypoglycemic medications is associated with avoidance of hospitalizations, and to identify adherence thresholds for optimal discrimination of hospitalization risk.

Methods—Retrospective cohort study of 33,130 non-dual-eligible Medicaid enrollees with type 2 diabetes. We randomly selected 90% of the cohort (training sample) to develop the prediction algorithm and used the remaining (testing sample) for validation. We applied random survival forests to identify predictors for hospitalization and fit survival trees to empirically derive adherence thresholds that best discriminate hospitalization risk, using the proportion of days covered (PDC).

Outcomes—Time to first all-cause and diabetes-related hospitalization.

Results—The training and testing samples had similar characteristics (mean age, 48 years; 67% female; mean PDC 0.65). We identified eight important predictors of all-cause hospitalizations (rank in order): prior hospitalizations/emergency department visit, number of prescriptions, diabetes complications, insulin use, PDC, number of prescribers, Elixhauser index, and eligibility category. The adherence thresholds most discriminating for risk of all-cause hospitalization varied from 46% to 94% according to patient health and medication complexity. PDC was not predictive of hospitalizations in the healthiest or most complex patient subgroups.

Conclusions—Adherence thresholds most discriminating of hospitalization risk were not uniformly 80%. Machine-learning approaches may be valuable to identify appropriate patient-specific adherence thresholds for measuring quality of care and targeting non-adherent patients for intervention.

Keywords

medication adherence; diabetes; machine learning; survival tree; classification and regression tree

Introduction

Approximately 30 to 50% of U.S. adults do not adhere to chronic disease (e.g., diabetes) medications, leading to more than $100 billion in preventable costs annually.[1] Adherence is routinely measured based on prescription refills using administrative claims data. These refill adherence measures have been used to study the impact of medication non-adherence on clinical outcomes[2-4] and to predict health care costs and utilization.[5] Refill adherence is now an integral component of performance measurement for Medicare Part D plans, as well as commercial insurance plans, with substantial financial ramifications for health insurers, clinical practices, and pharmacies.[6]

Consistent long-term medication adherence is critical for disease management and the ultimate goal is to achieve 100% adherence. However, lower thresholds for acceptable adherence are often chosen for quality improvement and measurement activities. The most commonly used threshold for defining ‘good’ adherence is 80%, meaning that patients have medication on hand at least 80% of the time. The evidence for use of the 80% threshold is limited, and its history is traced back to a blood pressure treatment trial of 230 steelworkers in 1975.[7] Nonetheless, the threshold is now uniformly used for quality measurement.[6, 8] In

reality, the most clinically meaningful adherence threshold may vary by disease, medication class or intensity, patient sub-groups, target clinical outcomes, or adherence measures.[2] Applying the 80% threshold uniformly to all diseases and medications without any validation may lead to misallocation of resources for improving health outcomes.[9, 10]

In contrast to expert- or data-distribution driven (e.g., median) approaches for categorizing variables, outcome-oriented methods (e.g., machine-learning) are better suited for identifying optimal thresholds that best differentiate patients with respect to outcomes of interest.[11] Survival trees and random survival trees, extensions of classification and regression trees, are algorithmic machine-learning approaches that are designed for identifying discriminating predictors of survival or time-to-event data.[12] Survival trees identify mutually exclusive subgroups with a greater level of homogeneity whose members share characteristics/predictors of the outcome of interest (e.g., hospitalizations). Major advantages of survival trees over traditional modeling approaches include no assumptions of linearity and ability to handle complex interactions.[12, 13] Instead of using arbitrarily defined cutpoints, survival trees identify the cutpoints in binary predictors that most differentiate the outcome of interest.

To date, no studies have examined the optimal adherence thresholds overall or within different patient subgroups using novel machine-learning approaches. In this study, we identify important predictors of hospitalizations and examine the adherence thresholds to oral hypoglycemics that are most discriminating of hospitalization risk in diabetes patients. Our study setting was the Pennsylvania Medicaid program, the 6th largest program in the US by enrollment and the 4th largest by expenditure.[14] Our findings may shed light on the appropriateness of adherence performance targets built into private and public insurance plans and enable more individualized treatment decisions among diabetes patients.

Methods

Study Design, Data Sources and Study Cohort

This study was a retrospective longitudinal analysis of Pennsylvania Medicaid administrative claims data for all fee-for-service and managed care enrollees from 2007 to 2011. Enrollment varied annually from 2.2 to 2.6 million. Enrollment files contain demographic data (e.g., age, gender, race), eligibility category, and dates of enrollment. The dataset includes all Medicaid claims and encounter data for outpatient, inpatient, long-term care, and professional services as well as prescription drug claims. The prescription drug file contains the record of all prescriptions reimbursed by Medicaid, including national drug codes, date of prescription fill, quantity dispensed, days of supply, and prescriber information. This study was deemed exempt from review by our Institutional Review Board.

We limited our analyses to enrollees aged 18-64 years who were not dually enrolled in Medicare, because we were not able to observe their prescription drug utilization. We identified type 2 diabetes patients based on the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes 250.0x through 250.9x (where x=0 or 2) from outpatient, inpatient, or professional claims and/or having any oral hypoglycemic claims.[15] An index date was defined as the date of a patient's first prescription

fill for oral hypoglycemics between 07/01/2007-12/31/2009 with no oral hypoglycemic prescriptions in the 6 months prior. We followed each patient's refill claims for 12 months following the index date. Patients were required to have at least 18 months of continuous Medicaid enrollment (i.e., at least 6 months pre-index date as baseline period and 1 year post) to obtain information on predictor variables and allow for complete follow-up. We further excluded patients who had 1) less than two oral hypoglycemic fills during the "index year" (i.e., 12 months following the index date), 2) a diagnosis of gestational diabetes, 3) metformin used for polycystic ovary syndrome only, or 4) evidence of prolonged institutionalization (i.e., cumulative nursing home or inpatient stay ≥ 90 days) during the index year, given that their medications were administered by nurses or caregivers (eFigure 1).

Exposures: Adherence to Oral Hypoglycemics

Based on dispensing date and days supplied, we calculated an interval-based proportion of days covered (PDC) with oral hypoglycemics over a 1-year period starting from the index date.[6, 16] All oral hypoglycemics dispensed within a therapeutic class (e.g., glyburide and glipizide in the sulfonylurea class) were considered interchangeable. For those having concurrent prescriptions of multiple oral hypoglycemic classes, we calculated an average of the prescription-based PDC across oral hypoglycemic classes and then generated a group mean of these averages over a 1-year period for each patient.[16] The prescription-based PDC for all drugs within a class was defined as the number of days covered with oral hypoglycemics between the first and last prescriptions during the index year (numerator) divided by the number of days between the first and last prescriptions plus the accumulated days supplied from the last prescription (denominator).[16] When a dispensing occurred before the previous dispensing should have run out, utilization of the new oral hypoglycemic fill was assumed to begin the day after the end of the previous dispensing. Thus, PDC values were truncated at 1.0. The Pharmacy Quality Alliance has selected PDC as their preferred method of calculating chronic medication adherence over medication possession ratio (MPR), which may overestimate the true pharmacy refill rate.[17] In addition, we adjusted PDC for inpatient stays, as recommended by Medicare.[6]

Outcomes and Measures: Hospitalizations

Our primary outcome variable was time to first all-cause hospitalization "in the 12 months after the index year" (i.e., between 12-24 months after the index date). We chose all-cause hospitalization as our primary outcome because prior studies have showed that medication non-adherence may manifest as numerous different adverse health outcomes (e.g., falls, infections), which increase costs and risks of all-cause hospitalization.[4, 18, 19] Our secondary outcome was time to first diabetes-related hospitalization in the 12 months after the index year. Diabetes-related hospitalizations included inpatient admissions for diabetes, hyperglycemia, hypoglycemia, infections, electrolyte imbalance, diabetes retinopathy, nephropathy and neuropathy, ischemic heart disease, stroke, or peripheral circulatory disorder and were identified by a qualifying ICD-9 code as the primary discharge diagnosis or current procedural terminology (CPT) codes in any position, similar to prior studies (eTable 1).[20, 21]

Predictors

Our predictors of hospitalization, including sociodemographics, measures of service use and health status, were based on prior studies of medication adherence.[22-25] We focused on factors measured on or before the initiation of oral hypoglycemics to assess the prediction accuracy that was possible before observing any follow-up and to avoid including as predictors changes in patient health status that may themselves be consequences of the use (or nonuse) of oral hypoglycemics. Sociodemographic factors included age, gender, race (white, black, Hispanic or others), type of health plan (fee-for-service or managed care plan), and Medicaid eligibility category (General Assistance [GA], Supplemental Security Income [SSI], Temporary Assistance for Needy Families [TANF], and Waiver]). The General Assistance category is a medically needy group not eligible through traditional Medicaid whose care is financed only by state funds. We included several measures of service use on or within 6 months before the index date including number of outpatient visits, inpatient or emergency department (ED) utilization, number of unique prescribers, average monthly number of prescriptions, and number of pharmacies.[23] Health status factors included patient comorbidity defined by the Elixhauser's comorbidity index (excluding diabetes, total score range: 0 to 29),[26] and diabetes severity defined by the diabetes complications severity index (DCSI, range 0-13) during the baseline period.[27] We also defined diabetes treatment intensity by calculating the number of anti-diabetic medication classes and days receiving prescriptions for insulin during the index year.

Statistical Analysis

Overview—Our analysis followed three steps. First, we applied random survival forests to identify important predictors for hospitalization using the training sample. Second, we fit a survival tree to examine the adherence thresholds to oral hypoglycemics using the training sample. Third, we validated the algorithm derived from the training sample using the independent testing sample.[28] All statistical analyses were performed with SAS® 9.3 (SAS Institute Inc., Cary, NC) and R version 3.0.2 (www.R-Project.org). We constructed survival trees using the *Recursive Partitioning and Regression Tree (RPART)* R package,[29] and random survival forests using the *RandomSurvivalForest (randomForestSRC)* R package.[30] Details can be found in the technical appendix **(eMethod)**.

Random Survival Forests—Details of random survival forest techniques are described elsewhere and in the technical appendix.[30-32] The gold-standard for validation is using an external sample with similar population characteristics or splitting data into two independent subsets.[12] Therefore, we randomly selected 90% of the cohort as the training sample to develop a prediction algorithm for hospitalization risk, and used the remainder as an independent testing sample to validate the developed algorithm.

Random survival forests,[31] consisting of numerous independent survival trees, were developed to improve prediction stability over a single tree.[31] To obtain the most important predictors of hospitalization risk, we constructed a random survival forest of 1,000 survival trees, where each tree was from an independent and unique bootstrap sample of the training sample.[32] From these 1,000 survival trees, we identified important variables by averaged minimal depth from the tree trunk (i.e., split nodes nearest to the root node) for each

variable. The smaller the minimal depth, the greater the association with the dependent variable and hence the impact of that variable on prediction. Simply due to random chance, a variable with no predictive power may on occasion split at a lower depth when a large number of trees are grown. Thus, we used the average minimal depth of such a variable, determined in prior work, [33] as a threshold to identify a set of important predictors whose average minimal depths were less than the said threshold.[33]

We assessed the prediction accuracy by the Harrell concordance index (*C*-index) using the out-of-bag method (i.e., bootstrap 2/3 sample of the training sample).[31, 34] *C*-index can be interpreted as the probability that a patient from the event group has a higher predicted probability of having an event than a patient from the non-event group. The error rate is 1-*C*. A small prediction error is preferred; however, there is no gold standard for how small would be desirable. Previous studies have reported prediction error rates ranging from 25-40%, indicative of the complexity of predicting health outcomes.[28, 32, 35] In these studies, random survival trees performed at least as good as or better than traditional models.[28, 32, 35]

Survival Trees—We then fit survival trees with the important predictors identified from random survival forests and explored their optimal thresholds for discriminating hospitalization risk.[12] Briefly, survival trees start with the root node that includes all patients from the training sample and uses binary recursive partitioning to systematically search among all predictors and all possible thresholds that classify or segment a target population into increasingly homogeneous subgroups with respect to hospitalization risk. For continuous variables (e.g., PDC), it searches over all threshold values to identify the one that optimally splits patients into groups with similar likelihood of hospitalization risk. Partitioning stops when risks for hospitalizations for the two partitioned subgroups are not statistically different based on log-rank tests or the minimum terminal node size is less than 20 patients. In addition, we pruned the tree with 10-fold cross-validation methods to guard against model over-fitting (complex parameter=0.005). We calculated hazard ratios (HR) for each identified subgroup. We compared *C*-indices between the survival tree and Cox proportional hazard model (with the same predictors selected) to assess prediction performance.[34, 36] Finally, we compared Akaike's Information Criterion (AIC) obtained from our model and those of traditional models with different overall fixed thresholds.

Validation of Prediction Models in the Testing sample—To ensure the robustness of the results, we applied the algorithm derived from the survival tree in the training sample to the testing sample, and calculated the *C*-index to evaluate prediction performance of the testing sample.

Results

Baseline Characteristics

Baseline characteristics were similar (all $p > 0.05$) between the training (n=29,855) and testing samples (n=3,275) (Table 1). For those in the training sample, mean age was 48.3 years, 67% were women, 52% were white and 28% were black, 71% enrolled in the Medicaid program through SSI, and 39% had at least one hospitalization or ED visit in the

six months before their index oral hypoglycemic fill. Twenty-seven percent had at least one prescription fill for insulin during the index year.

Oral Hypoglycemic Use, Adherence and Hospitalizations

Training and testing samples had similar patterns in the use of oral hypoglycemics, and adherence and hospitalization rates. On average, patients had prescription fills for 1.9 (SD 0.9) different oral hypoglycemic classes during the index year. Biguanides (79%), sulfonylureas (44%), and thiazolidinediones (22%) were the most commonly prescribed oral hypoglycemic classes. The mean PDC was 0.65 (SD 0.26), and 38% of the sample reached the 80% adherence threshold during the index year. One-quarter (training=24%; testing=24.7%) had all-cause hospitalizations (median months to event= 4.7) (eTable 2). Approximately 13% of patients had diabetes-related hospitalizations (median months to event= 5.6).

Predictors and Adherence Thresholds for All-Cause Hospitalizations

Eight important predictors of all-cause hospitalizations were identified from random survival forests, ranked in order of predictive importance: prior hospitalizations or ED visits, number of monthly prescriptions, DCSI, insulin use, PDC, number of prescribers, Elixhauser index, and Medicaid eligibility category Figure 1). The average error rate was 27% from a random survival forest with 1,000 trees.

Figure 2 illustrates the first two splits extracted from the final pruned survival tree. The first split, the most important predictor, is based on the presence/absence of prior hospitalizations or ED visits. Of the 29,855 patients in the root node, 7,160 (24.0%) had a hospitalization. For those with no prior hospitalizations/ED visit (left branch), use of insulin for >90 days was the next most important predictor of hospitalization. Of the 13,801 individuals without chronic insulin use (node I), 2,207 (16.0%) had a hospitalization, whereas of the 4,399 with chronic insulin use (node II), 1,109 (25.2%) had a hospitalization.

Figure 3 shows the full survival tree classifying patients into subgroups with distinct risk of all-cause hospitalizations based on their predictor combinations. The adherence thresholds to oral hypoglycemics most discriminative of all-cause hospitalization risk varied from 46% to 94%, based on patient subgroups (PDC thresholds highlighted in red in Figure). For example, among individuals who had no prior hospitalizations or ED visits, had insulin prescriptions ≥90 days, and did not have more than 13 prescriptions per month, the tree identified 59% as the PDC threshold that most differentiates two groups with hospitalization risk (terminal nodes F and G in Figure 3). Of the 2,130 individuals in the terminal node F, the median PDC was 0.84, and 441 (20.7%) had a hospitalization (HR 1.64; 95% CI: 1.46-1.83, compared to node A). Of the 1,728 individuals in node G, the median PDC was 0.40, and 495 (28.6%) had a hospitalization (HR 2.39, 95% CI: 2.16-2.67, compared to node A). eTable 3 summarizes the mean/median PDC and hazard ratios for each terminal node.Table 2 summarizes the identified adherence thresholds for various patient subgroups and their associated risks of hospitalization, comparing those above and below the identified threshold. For example, using the 59% adherence threshold, individuals in node F had 32% lower risk of hospitalization than those in node G (HR 0.68, 95% CI: 0.60-0.77).

The survival tree identified a discriminating PDC threshold for 12 out of 17 subgroups (*n*=16,026 [53.7% of the training cohort]). However, PDC was not predictive in healthier patients (e.g., terminal nodes A and B individuals with no prior hospitalizations or ED visits, no insulin prescriptions or < 90 days, monthly prescriptions ≤7) nor in patients with complex health conditions (e.g., terminal node Q: individuals with prior hospitalizations or ED visits, DCSI ≥1, and monthly prescriptions≥13).

The survival tree for predicting all-cause hospitalizations performed better than a Cox proportional hazard model with same predictors (error rates: 26% vs. 33%, eTable 4). The error rate was 27% when applying the same predictors and algorithm derived from the training sample to the testing sample. The survival tree model resulted in an AIC reduction of over 29% over Cox models with fixed overall thresholds in the 60-95% range.

Predictors and Adherence Thresholds for Diabetes-Related Hospitalizations

Seven predictors of diabetes-related hospitalizations were identified, including insulin use, DCSI, prior hospitalizations or ED visits, number of monthly prescriptions, PDC, Medicaid eligibility and age (eFigure 2). The adherence thresholds to oral hypoglycemics most associated with diabetes-related hospitalization risk varied from 59% to 92% across subgroups of health and treatment complexity (eFigure 3 and eTables 5-6).

Discussion

Using a novel machine-learning approach, we demonstrate that the adherence thresholds most predictive of hospitalization risk are not uniformly 80%. The thresholds vary from 46% to 94% according to patient health and medication complexity, among those for whom adherence was a significant predictor of hospitalization. For both the healthiest and sickest/most complex patients, refill adherence lacked a predictive association for all-cause hospitalizations when added to other markers of health status and diabetes severity readily available in claims data, such as a history of prior hospitalizations. The routine application of an 80% threshold for identifying and intervening on poor adherence may thus be inefficient. While achieving 100% adherence should be the ultimate goal for chronic disease management, machine learning approaches may be an avenue for identifying more refined adherence thresholds for policy and quality improvement efforts.

Survival trees and random survival forests have been applied successfully to identify important predictors in numerous clinical fields such as cancer and genomics research.[28, 37-39] To our knowledge, this is the first study that identified empirically-derived adherence thresholds and included complex interactions between predictors using machine-learning approaches. Several studies have attempted to define optimal adherence cutpoints using arbitrarily defined thresholds or intervals (e.g., 80%) in traditional models (e.g., logistic models).[5, 40-48] However, traditional modeling approaches neither handle complex interactions among predictors nor take into account nonlinear effects.[49] Other appealing features of machine-learning approaches are that 1) assumptions (e.g., proportional hazards) or selection methods/criteria of important variables (e.g., stepwise regression) are not required, 2) surrogate splits are used to handle missing data, and 3) tree-structured plots illustrating the importance and relationship of predictors are intuitive and easy to apply in

clinical settings.[49] Nevertheless, traditional modeling may outperform machine learning when nonlinearity or complex interactions do not exist. A factor is predictive based not only on the magnitude of the relative risk but also on the prevalence of the factor and the outcome. A predictor might not be selected in the tree model if its prevalence or the prevalence of the outcome is extremely low. Machine-learning approaches are valuable tools to identify important predictors and optimal adherence thresholds of medications of interest, especially when complex interactions among participant characteristics and adherence thresholds exist.

Among patients who had prior hospitalizations/ED visits, and monthly prescriptions <7 in our analysis, the adherence thresholds were higher than 80% (94% for those without diabetes comorbidities and 83% for those with diabetes comorbidities). A previous study using logistic regression also showed adherence thresholds were 89% and 84% for avoidance of all-cause and diabetes-related hospitalizations among those with a single oral hypoglycemic therapy, which likely reflects patients with less severe diabetes and treatment complexity.[40] Despite differences in study design and cohorts, our study and the study by Karve et al illustrate the challenge of using an 80% threshold for all patients. Among these healthier patients, achieving adherence of 80% may not be sufficient to optimally reduce the risk of hospitalization.

Relatedly, using a uniform 80% threshold for identifying targets for adherence intervention for individuals with higher comorbidity or medication burden may not be the most efficient use of resources to optimize hospitalization risk, given the lower identified adherence thresholds and other markers readily available in claims data that were more predictive of hospitalizations. Focusing away from the 80% threshold, however, runs counter to the incentives built into Medicare Star Ratings and other quality measures, and, ultimately, clinical trials are the ideal mechanism for truly determining the levels of adherence most associated with long-term health outcomes. Nonetheless, using machine-learning approaches to identify optimal adherence thresholds based on different patient characteristics may help inform long-term clinical trials of the impact of adherence on health outcomes and help payers and clinicians target proper interventions to improve adherence, better allocate resources, and ultimately improve disease management and outcomes.

Our study has several limitations. First, our prediction error rates ranged from 25%-27%. A possible explanation is that our study relied on administrative data and lacks clinical and socio-behavioral information (e.g., HbA1C) associated with adherence and hospitalizations. However, the variables included in the current study are typically available to payers who would be targeting adherence interventions. In addition, the prediction of our survival trees performed better than traditional Cox proportional hazard models and is in line with prior studies using random survival forests and survival trees.[28, 32, 35, 50] Second, it is unknown if and how the dispensed drugs were actually used by the patients. Patients who never filled their first prescription were also not captured.[24] These limitations may overestimate refill adherence. Third, similar to prior analyses, we were unable to account for adherence to other, non-diabetic medications, which could impact rates of hospitalization. Finally, the Medicaid population in Pennsylvania may not be generalizable to commercially insured or other Medicaid populations with a different demographic profile or with different

programmatic features. However, given the fact that the Pennsylvania Medicaid program has a gender distribution (42% male) and health care utilization and access similar to Medicaid nationally, it is likely to be reasonably representative.[25]

Conclusions

Our findings demonstrate that the 80% adherence threshold to oral hypoglycemics is not optimal for predicting risk of hospitalization among all patient subgroups. Refill adherence thresholds for measuring quality of care may need to be customized by disease and patient complexity. Our work shows that machine-learning approaches hold promise as an intuitive and powerful approach for optimizing health outcomes and customizing interventions in medication adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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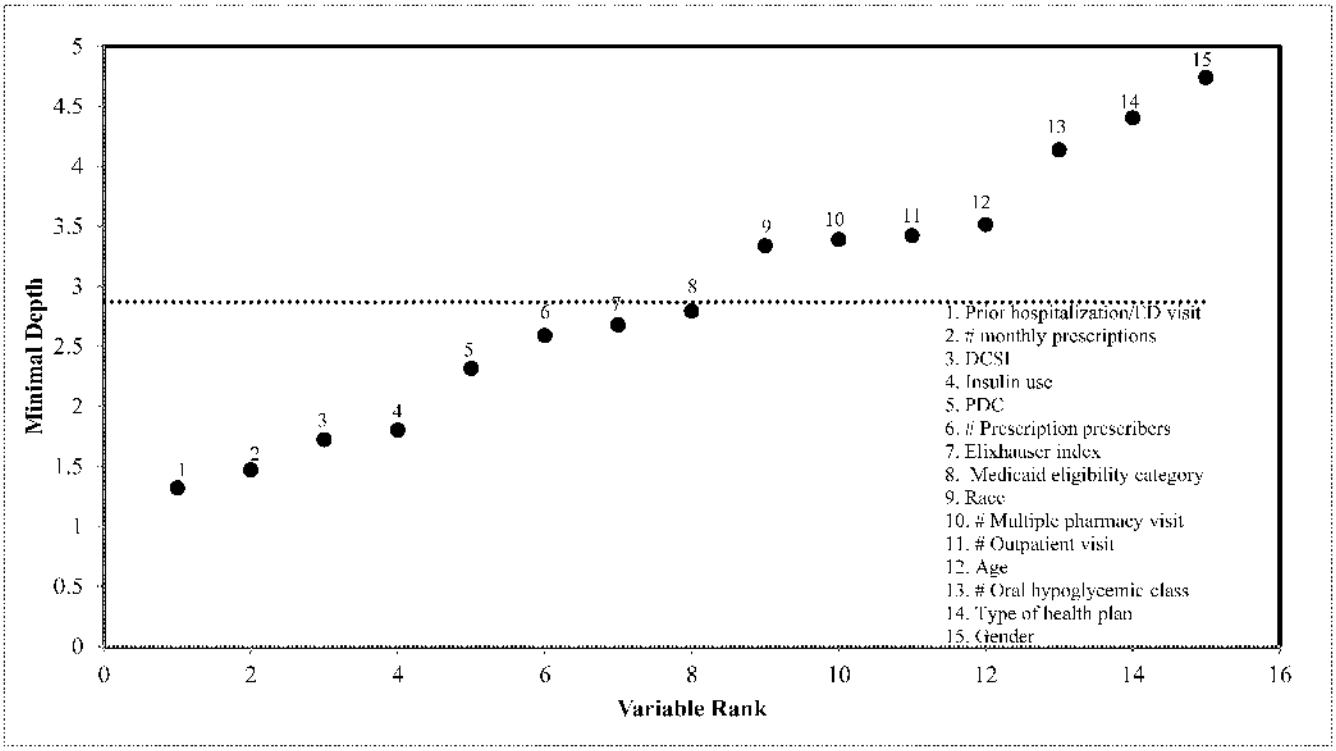

Figure 1. Important Predictors of All-cause Hospitalizations Selected by Minimal Depth from Random Survival Forests

Note: The figure represents average minimal depth (i.e., split nodes nearest to the root node) for each variable from 1,000 individual survival trees. The horizontal line represents the average minimal depth expected from an unrelated variable, and thus variables whose average minimal depth is below this threshold are considered important predictors.

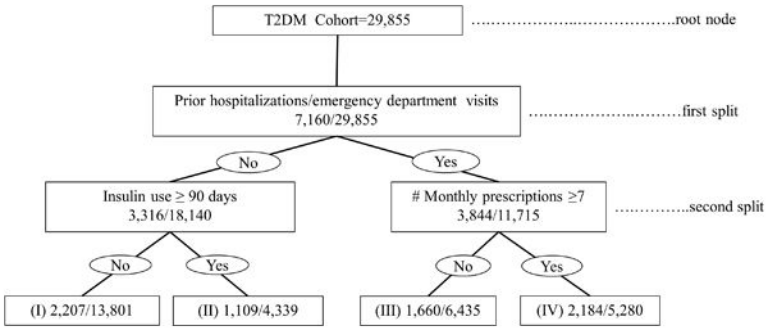

Figure 2. Survival Tree Illustration

Note: The numbers on the bottom of each node represent number of patients who had all-cause hospitalizations/total patients in that node. The most important predictor (first split) is prior hospitalizations/emergency department visits (presence vs. absence). The second important predictor for the left branch is insulin use ≥ 90 days (yes vs. no). In the leftmost intermediate node (I), of 13,801 patients without hospitalizations/emergency department visits or insulin use ≥ 90 days, 2,207 had all-cause hospitalizations.

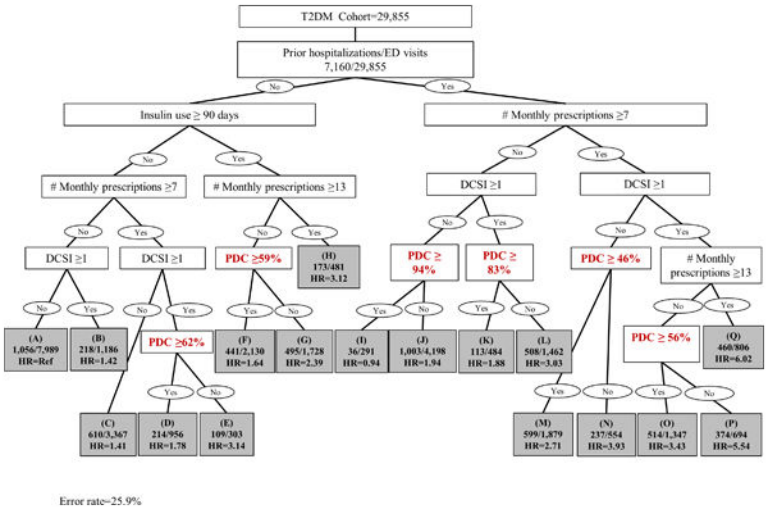

Figure 3. Survival Tree of Adherence Thresholds associated with Risk of All-Cause Hospitalizations

Abbreviations: DCSI: diabetes complication severity index; ED: emergency department; HR=hazard ratio; PDC: proportion days covered

Note: Nodes (A) to (Q) are terminal nodes. The numbers on the bottom of each node represent numbers of events/patients in that node.

Table 1
Characteristics of Training and Testing samples

Characteristics[a]	Training (N=29,855)	Testing (N=3,275)	P values[a]
Sociodemographics			
Age, Mean (SD)	48.3 (10.0)	48.1 (10.1)	0.33
Sex, n (%)			0.98
Female	19,851 (66.5)	2,177 (66.5)	
Male	10,004 (33.5)	1,098 (33.5)	
Race, n (%)			0.74
White	15,473 (51.8)	1,665 (50.8)	
Black	8,379 (28.1)	937 (28.6)	
Hispanic	4,529 (15.2)	504 (15.4)	
Others/unknown	1,472 (4.9)	169 (5.2)	
Type of health plan, n (%)			0.46
Fee-for-service	6,429 (21.5)	687 (21.0)	
Managed care	23,426 (78.5)	2,588 (79.0)	
Medicaid eligibility category, n (%)			0.51
General assistance	3,943 (13.2)	455 (13.9)	
Supplemental Security Income	21,294 (71.3)	2,296 (70.1)	
Temporary assistance for needy families	4,523 (15.2)	512 (15.6)	
Waiver	95 (0.3)	12 (0.4)	
Measures of service use			
Number of outpatient visits, mean (SD)	3.9 (8.3)	4.0 (11.1)	0.38
Prior hospitalizations or ED visits, n (%)	11,715 (39.2)	1,294 (39.5)	0.76
Number of monthly total prescriptions, mean (SD)	6.5 (4.1)	6.5 (4.0)	0.83
Number of unique prescribers, mean (SD)	2.7 (1.8)	2.7 (1.8)	0.73
Number of unique pharmacies, n (%)			0.56
Single	16,856 (56.5)	1,848 (56.4)	
Multiple	12,985 (43.5)	1,424 (43.5)	
Health status factors			
Diabetes complication severity index (range 0-13), mean (SD)	0.41 (0.8)	0.42 (0.8)	0.55
Number of anti-diabetic medication classes during the index year, mean (SD)	1.9 (0.92)	1.9 (0.93)	0.87
Had insulin fills during the index year, n (%)			0.22
0-<90 days	1,635 (5.5)	159 (4.9)	
≥ 90 days	6,447 (21.6)	734 (22.4)	
Elixhauser comorbidity index (excluding diabetes, range 0-29), mean (SD)	1.7 (1.7)	1.7 (1.8)	0.76
Adherence Rate			
PDC during the index year	0.65 (0.26)	0.64 (0.26)	0.29

Abbreviations: PDC: proportion of days covered; SD: standard deviation;

[a] Student's t test was used for continuous variables and X^2 test was used for categorical variables to compare characteristics between training and testing samples.

Table 2

Subgroups with PDC Thresholds Identified by Survival Tree and All-Cause Hospitalization Risks

Sub-group	Meaningful PDC threshold	% with hospitalization above PDC threshold (terminal node in Figure 3)	% with hospitalization below PDC threshold (terminal node in Figure 3)	HR of above vs. below PDC threshold (95% CI)
No history of hospitalizations or ED visits				
• No insulin use or insulin use < 90 days • ≥ 7 prescriptions per month • Had ≥ 1 diabetes complications	62%	22.4% (D)	35.9% (E)	0.52 (0.42, 0.64)
• Insulin use≥ 90 days • <13 prescriptions per month	59%	20.7% (F)	28.6% (G)	0.68 (0.60, 0.77)
Had history of hospitalizations or ED visits				
• < 7 prescriptions per month • No diabetes complications	94%	12.4% (I)	23.9% (J)	0.48 (0.34, 0.67)
• < 7 prescriptions per month • Had ≥ 1 diabetes complications	83%	23.3% (K)	34.7% (L)	0.62 (0.50, 0.76)
• ≥ 7 prescriptions per month • No diabetes complications	46%	31.9% (M)	42.8% (N)	0.69 (0.59, 0.80)
• ≥ 7 prescriptions per month • Had ≥ 1 diabetes complications • <13 prescriptions per month	56%	38.2% (O)	54.2% (P)	0.62 (0.54, 0.70)

Abbreviations: CI: confidence interval; ED: emergency department