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MACHINE LEARNING FOR INITIAL INSULIN DOSAGE PREDICTION IN HOSPITALIZED PATIENTS

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ABSTRACT: The study sought to determine whether the machine learning can predict initial inpatient total daily dose (TDD) of insulin from an electronic health records more precisely than existing guideline-based dosing recommendations. By Using electronic health records from a academic center between 2008 and 2021 of 16,848 inpatients receiving subcutaneous insulin dosage who achieved target blood glucose control level of 100-180 mg/dL on a day, we trained an ensemble machine learning algorithm that consists of regularized regression, random forest, gradient boosted tree models for 2-stage TDD predictions. We evaluated the ability to predict patients require more than 6 units TDD and their point-value TDDs to achieve the target glucose control. The method achieves of an area under the receiver-operating characteristic curve of an 0.85 (95% [CI], 0.84-0.87) and area under precision-recall curves of 0.66 (95% CI, 0.64-0.68 for the patients who require more than 6 units of TDD. For the patients requiring more than 6 units TDD, that mean absolute percent error in the dose prediction based on the standard clinical calculators using patient weight is in range of 136%-329%, while the regression model based on the weight improves to the 60% (95% CI, 57%-63%), and the full ensemble model that further improves to 51% (95% CI, 48%-54%). Machine learning approaches based on totally readily available electronic medical records that can discriminate which inpatients require more than 6 units TDD and estimates individual doses are more accurately than standard guidelines and practices.

Keywords- *machine learning, diabetes mellitus, insulin.*

1. INTRODUCTION

Poorly controlled glucose is both common and dangerous in hospitalized patients, reflecting deficiencies in common standard practices in insulin dosing. Hyperglycemia, defined as a blood glucose >140 mg/dL, occurs in 22% to 46% of non–critically ill hospitalized patients,1 and can lead to serious complications, including infections, cardiovascular events, and increased overall mortality.2 The increased odds of mortality among patients with a blood glucose above 145 mg/dL is 1.3 to 3 times that of patients with normal glucose (70-110 mg/dL), independent of illness severity.3 The treatment for hyperglycemia in inpatients is insulin, a hormone essential to enabling cells to uptake glucose from the blood for energy. However, insulin has a narrow therapeutic window when given as a medication, and overtreatment can lead to dangerous hypoglycemia causing seizure, arrhythmia, or even death. As such, predicting an accurate insulin dose is critical for clinical outcomes. The existing standard of care for estimating initial insulin dose prediction is unfortunately highly variable, as it is typically driven mainly by individual clinical judgment

supplementing crude weight-based clinical calculators, often leading to ineffective glucose control.4 Practice guidelines for inpatient insulin dosing primarily revolve around weight-based clinical calculators that estimate the total daily dose (TDD) of insulin required to be 0.4 to 0.6 units/kg among nonelderly patients with good kidney function.5,6 This calculator results in a range of dosing that can vary by 50%, requiring prescribers to use variable clinical experience to adjust for factors such as age, suspected insulin sensitivity, and renal function. Even in optimal conditions, existing TDD guidelines are based on a dosing schema of unclear provenance chosen in published studies7 that have not been clinically validated. The current practice leads to significant dosing heterogeneity even within the same patient's hospitalization.

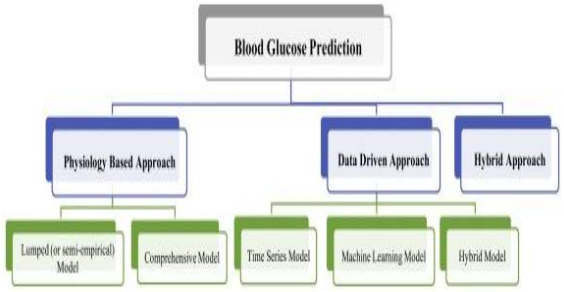

Fig.1: Taxonomy of blood glucose prediction approaches

For admitted patients, prescribing an initial insulin dose is often challenging, as there is limited information available at this early stage, whereas titration is often a simpler problem because a patient's insulin sensitivity can be estimated from their response to previous insulin doses. Specialized glucose management services have been established to help minimize both hyperglycemia and hypoglycemia in the inpatient setting. These consult services have improved blood glucose control and cost savings.9,10 However, the number of patients who need consults often exceeds the capacity of these services.11 Decision support that assists in insulin dosing could improve inpatient glycemic control at scale. An alternate approach to formal consult services is a remote glucose monitoring service in which a consulting endocrinologist provides teams with insulin dosing suggestions based on chart review, without examining the patient, which has shown success in reducing the proportion of patients with hyperglycemia and reducing hypoglycemic events.12 The success of such remote glucose control programs suggests that electronic health records may contain sufficient information for prescribing insulin, and can be leveraged using automated machine learning methods.

2. LITERATURE REVIEW

2.1 Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline [1] :

The aim was to formulate practice all guidelines on the management of hyperglycemia in the hospitalized patients in the non-critical care setting. The Task Force was the composed of a chair, selected by Clinical Guidelines of Subcommittee of Endocrine Society, and six additional experts, and methodologist. This evidence-based guideline that was developed using the Grading of all Recommendations, Assessment, Development, and Evaluation (GRADE) system that to describe both the strength of recommendations and the quality of the evidence. One of group meeting, several conference calls, and an e-mail communications of enabled consensus. Endocrine Society members,an American Diabetes Association, an American Heart Association, an American Association of Diabetes Educators, an European Society of Endocrinology, and Society of Hospital Medicine reviewed and commented on preliminary drafts of this guideline. Hyperglycemia is common, costly , and serious health care problem in the hospitalized patients. Observational and randomized controlled the studies indicate that the improvement in glycemic control results in lower rates of the hospital complications in general medicine and surgery patients. Implementing of a standardized sc insulin order set promoting in the use of the scheduled basal and the nutritional insulin therapy is the key intervention in inpatient management of the diabetes. We provide recommendations for the practical, achievable, and safe glycemic targets and describe protocols, procedures, and system improvements required to the facilitate of the achievement of glycemic goals in patients with the hyperglycemia and diabetes are admitted in non-critical care settings.

2.2 Management of inpatient hyperglycemia and diabetes in older adults. [2]:

Adults aged 66 years and older are fastest growing the segment of the U.S. population, and their number is expected to the double to 89 million between 2010 and 2050. The prevalence of the diabetes in the hospitalized adults aged 65-75 years and over 80 years of age has been estimated to be 25% and 40%,

respectively. Similar to the general populations, the presence of the hyperglycemia and diabetes in elderly patients is associated with increased risk of the hospital complications, longer length of the stay, and increased mortality compared with subjects with the normoglycemia. Clinical guidelines recommend target blood glucose between the 140 and 180 mg/dL (7.8 and 10 mmol/L) for most patients in intensive care unit (ICU).An similar blood glucose target is recommended for patients in the non-ICU settings; however, glycemic targets should be the individualized in the older adults on basis of the patient's clinical status, risk of hypoglycemia, and presence of diabetes complications. Insulin is the preferred agent to the manage hyperglycemia and diabetes in hospital. Continuous insulin infusion in ICU and rational use of basal-bolus or basal plus supplement regimens in non-ICU settings are effective in achieving glycemic goals. Noninsulin regimens with use of dipeptidyl peptidase 4 inhibitors alone or in combination with basal insulin have been shown to

safe and effective and may that represent an alternative to the basal-bolus regimens in elderly patients. Smooth transition of care to outpatient setting is facilitated by providing oral and written instructions regarding timing and dosing of insulin as well as education in basic skills for home management.

2.3 Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. [3] :

Hyperglycemia during critical illness is common and is an associated with the increased mortality. And Intensive insulin therapy has improved outcomes in the some, but not all, intervention trials. It is unclear whether the benefits of treatment differ among specific patient populations. The purpose of the study was to determine the association between hyperglycemia and risk- adjusted mortality in the critically ill patients and in separate groups stratified by the admission diagnosis. A secondary purpose was to determine whether mortality risk from hyperglycemia varies with intensive care unit type, length of stay, or diagnosed diabetes. The association between hyperglycemia and mortality implicates hyperglycemia as a potentially harmful and correctable abnormality in critically ill patients. The finding that hyperglycemia-related risk varied with admission diagnosis suggests differences in the interaction between specific medical conditions and injury from hyperglycemia. The design and interpretation of future trials should consider the primary disease states of patients and the balance of medical conditions in the intensive care unit studied.

2.4 Randomized study of basalbolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 Trial). [7]:

We sought to study optimal management of the hyperglycemia in all non-intensive care unit patients with the type 2 diabetes, as few studies thus far have focused on the subject. We conducted an prospective, multicenter, randomized trial to compare to the efficacy and safety of a basal-bolus insulin regimen with that of the sliding-scale regular insulin (SSI) in patients with type 2 diabetes. A total of the 130 insulin-naive patients were randomized to the receive glargine and glulisine (n = 65) or an standard SSI protocol (n = 65). SSI was taken four times per day for the blood glucose >140 mg/dl. Treatment with insulin glargine and glulisine are resulted in the significant improvement in the glycemic control that compared with that achieved with the use of the SSI alone. Our study indicates that the basal-bolus insulin regimen is the preferred over SSI in management of the non-critically ill, hospitalized patients with type 2 diabetes.

2.5 Glucose management in hospitalized patients [8]:

Glucose management in the hospitalized patients poses challenges to physicians, including identifying the blood glucose targets, judicious that use of the oral diabetes mellitus medications, and all implementing appropriate of insulin regimens. Uncontrolled blood glucose levels that can lead to deleterious effects on the wound healing, increased risk of the infection, and delays in the surgical procedures or discharge from hospital. Previously that recommended strict blood glucose targets for the hospitalized patients result in more cases of the hypoglycemia without improvement in patient outcomes. The current target is the 140 to 180 mg per dL. Use of the oral diabetes medications, particularly metformin, in the hospitalized patients is the controversial. Multiple guidelines that recommend stopping these medications at admission because of the inpatient factors that can able to increase the risk of renal or hepatic failure. However, oral diabetes medications that have important nonglycemic benefits and to reduce the risk of the widely fluctuating blood glucose levels. There is no proven risk of the lactic acidosis from metformin in the patients with the normal kidney function, and that can be used safely in many hospitalized patients with the diabetes. In Insulin dosing depends on patient's

previous experience with insulin, baseline diabetes control, and the renal function. On other considerations include the patient's current oral intake, comorbidities, and other medications. Many patients that can be managed using only the basal insulin dose, whereas others benefit from the additional short-acting premeal doses. Historically, sliding the scale insulin regimens that have been used, but they have not no proven benefit, increase in the risk of hypoglycemia and large fluctuations that in the blood glucose levels, and are not recommended that.

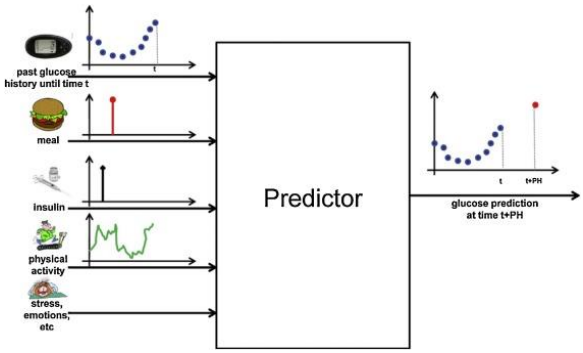

Fig.2: Data driven model

2.6 Retrospective study of inpatient diabetes management service, length of the stay and 30-day readmission rate of the patients with diabetes at a community hospital. [9]:

Hospitalized patients with the diabetes are at risk of complications and longer length of the stay (LOS). Inpatient Diabetes Management Services (IDMS) are also known to be an beneficial; however, their impact on patient care measures in the community, non-teaching hospitals, is unknown. To evaluate whether the co-managing patients with diabetes by the IDMS team reduces LOS and has 30-day readmission rate (30DR). This retrospective quality improvement cohort study had analyzed LOS and 30DR among all patients with the diabetes admitted to the community hospital. The IDMS medical team that consisted of an endocrinologist,and nurse practitioner, and the diabetes educator. The comparison group consisted of the hospitalized patients with the diabetes under standard care of the attending physicians (mostly internal medicine-trained hospitalists). The relationship between the study groups and outcome variables was assessed using Generalized Estimating Equation models. 4,654 patients with the diabetes (70.9 ± 0.2 years old) were admitted between January 2017 and May 2018. The IDMS team co-managed 18.3% of the patients, mostly with the higher severity of illness scores ($p < 0.0001$). Mean LOS in the patients co-managed by IDMS team decreased by 27%. An Median LOS decreased over time in IDMS group ($p = 0.046$), while there is no significant decrease was seen in comparison group. Mean 30DR in the patients co-managed by the IDMS decreased by the percent 10.71%. Median 30DR decreased among the patients co-managed by IDMS ($p = 0.048$). In an community hospital setting, LOS and 30DR slightly decreased in the patients that are co-managed by the specialized diabetes team.

3. IMPLEMENTATION

Prior research in the use of machine learning for diabetes-related problems has mostly focused on detecting adverse glycemic events and predicting blood glucose and insulin bolus doses using continuous glucose monitoring measurements in outpatients and has been limited to short-term predictions under 60 minutes. Studies predicting insulin bolus doses have focused on titration, adjusting previous insulin doses and relying on manual physician calculation. Although they showed promising results for outpatient type 1 diabetes management, these studies used either simulated data or evaluation metrics focused on glycemic control and not direct assessment of predicted insulin doses from patient data. These algorithms may not apply to hospitalized patients who are more clinically unstable than outpatients, and only have noncontinuous blood glucose checks typically no more than 4 times per day.There have been no prior studies predicting actual insulin doses in inpatients, although one study predicting what dose of insulin clinicians would order yielded an error of approximately 73%. Common machine learning methods used in prior diabetesrelated research include multivariate regression, support vector regression, and deep learning, though no method has been consistently shown to be superior. Instead of choosing a single algorithm, an ensemble machine learning approach, such as the Super Learner that we apply here, uses a weighted combination of multiple learning algorithms to achieve better predictive performance

than any single algorithm alone.

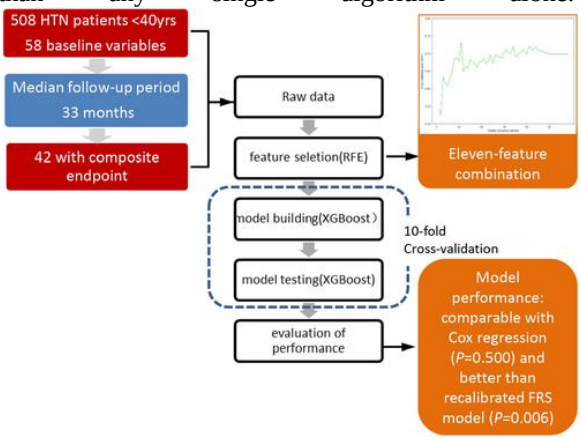

Fig.3: Machine learning model

Risk stratification of younger patients with hypertension that remains challenging. Generally, machine learning is considered as a promising alternative to the traditional methods for the clinical predictions as it is capable of processing large amounts of data. Therefore explored the feasibility of an machine learning approach for predicting outcomes in younger patients with hypertension and also compared its performance with the approaches now commonly used in clinical practice.

Our objective is to determine whether initial inpatient insulin requirements could be more accurately predicted from readily available electronic health record data using machine learning methods than existing weight-based guidelines. In stage I, we predicted whether a patient will require more than 6 units of TDD, ie, “low” vs “higher” insulin users, as a binary prediction. In stage II, for patients who require more than 6 units of TDD, we predicted the point-value TDD that the patients required to achieve good glucose control.

5. ALGORITHMS

We trained an ensemble machine learning algorithm that consisting of regularized regression, random forest, gradient boosted tree models for 2-stage TDD prediction.

REGULARIZED REGRESSION:

Regularization refers to the techniques that are used to calibrate machine learning models in order to minimize that the adjusted loss function and prevent either overfitting or underfitting. By using Regularization, we can able to fit our machine learning model appropriately on a given test set and hence that reduces the errors in it.

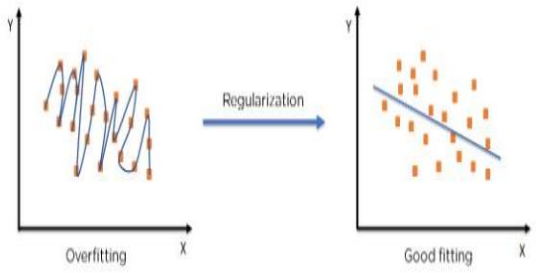

Fig.4: Regularization on an over-fitted model

There are two types of regularization techniques: 1)Ridge Regularization and.2) Lasso Regularization.

Ridge Regularization : It is also known as Ridge Regression and it modifies the either over-fitted or under fitted models by appending the penalty equivalent to sum of the squares of magnitude of the coefficients. Like means that the mathematical function representing to our machine learning model is minimized and all coefficients are calculated. The magnitude of the coefficients is squared and all added. Ridge Regression performs the regularization by shrinking all the coefficients present.

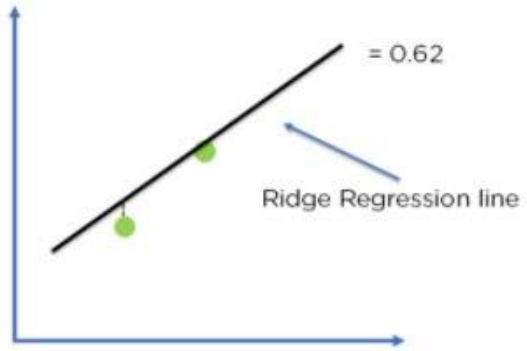

Fig.5: Ridge regression model

Lasso Regression: It modifies the either over-fitted or under-fitted models by appending the penalty equivalent to sum of absolute values of coefficients. Lasso regression is also performs the coefficient minimization, but instead of using squaring the magnitudes of coefficients, it takes true values of the coefficients. This means that coefficient sum could be 0, because of the presence of the negative coefficients..

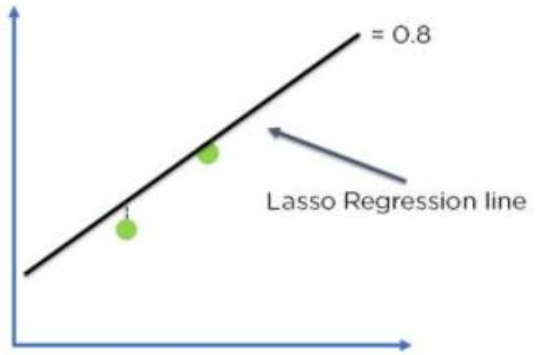

Fig.6: LASSO regression model

Random forest: It is a Supervised Machine Learning Algorithm that is used widely in Classification and Regression problems. It builds decision trees on different samples and takes their majority vote for classification and average in case of regression.

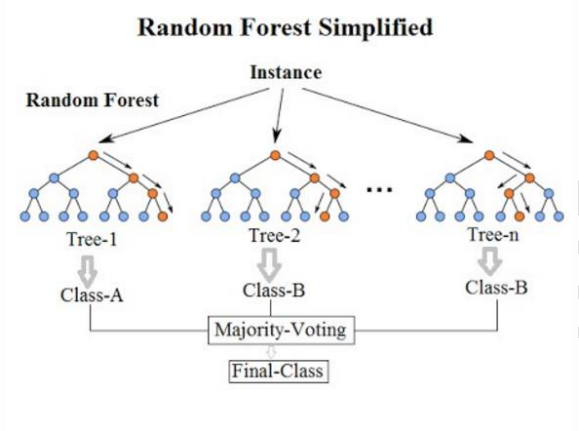

Fig.7: Random forest model

Gradient-boosted decision trees: Gradient Boosting is familiar with AdaBoost in that case they both use as an ensemble of the decision trees to predict a target label. However, as unlike AdaBoost, the Gradient Boost trees have a depth more larger than 1. In the practice, you'll typically see Gradient Boost that is being used with a maximum number of leaves of between 8 and 32 .

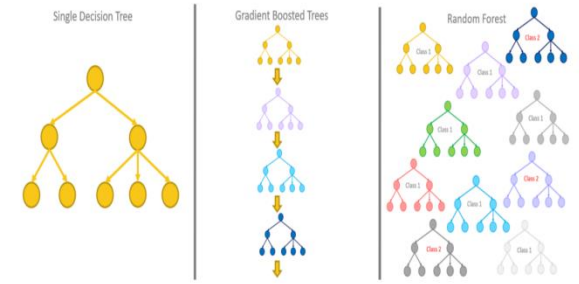

Fig.8: Gradient boosting tree model

5. EXPERIMENTAL RESULTS

Using electronic health record data from a tertiary academic medical center from 2008 to 2020, we retrospectively identified a cohort of unique patients who achieved target "good" glucose control during their most recent hospital encounters. Patients were considered as to have good control if they had at least 3 blood glucose measurements by glucometer that were within the target range of 100 to 180 mg/ dL6,33 on a calendar day without any measurement outside this range, consistent with inpatient diabetes management guidelines34 We excluded patients who were on total parenteral nutrition (TPN) or peripheral parenteral nutrition (PPN), tube feeds, insulin pumps, insulin infusions, or any rarely used insulin formulations (ordered fewer than 25 times in all records). Because insulin dosing is traditionally weight based, we also excluded patients with missing weights, about 2.4% of our original cohort. If patients had more than 1 good day, we selected the first good day of their most recent hospitalization.Included features were weight, height, age, sex, race, insurance status (public vs private), creatinine, diet (nothing by mouth, carbcontrolled, other), counts of microbiology lab orders, and amount of glucocorticoid use within the previous 48 hours. Hemoglobin A1c was classified into 4 categories: missing, <5.7, between 5.7 and 9, and >9 as normal, high, and panic high defined by our reference clinical laboratory.

	Mean	SD	Count	Proportion
Age, y	63.8	14.4		
Sex				
Female			7497	44.5%
Male			9351	55.5%
Weight, kg	84.1	24.0		
Height, cm	168.3	11.1		
Race				
Asian			2479	14.7%
Black			869	5.2%
Native American			71	0.4%
Pacific Islander			374	2.2%
White			9008	53.5%
Other			3562	21.1%
Unknown			485	2.9%
Insurance				
Public			10 129	60.2%
Private			6709	39.8%
Diet				
NPO			3323	19.7%
Carb controlled			3700	22.0%
Other			9825	58.3%
HbA1c, %	6.57	1.49		
Creatinine, mg/dL	1.40	1.42		
First glucose, mg/dL	148	62		
History of basal insulin use				
No			13 984	83.0%
Yes			2864	17.0%

Fig.9: Summary of demographics and some important variables in the full cohort

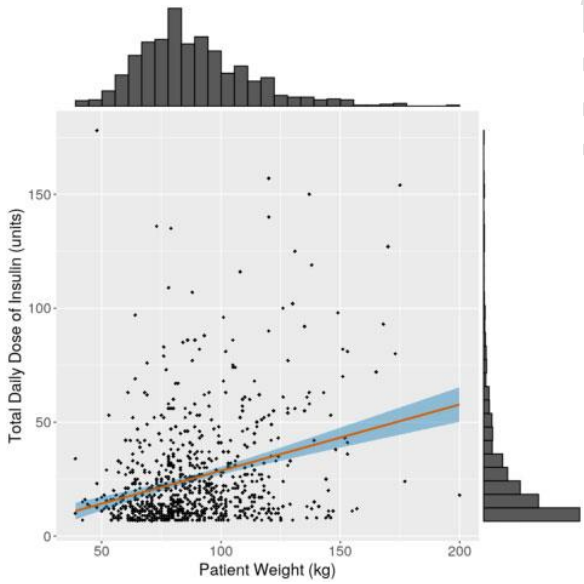

Fig.10: Plot of weight vs total daily dose with regression line and its confidence interval

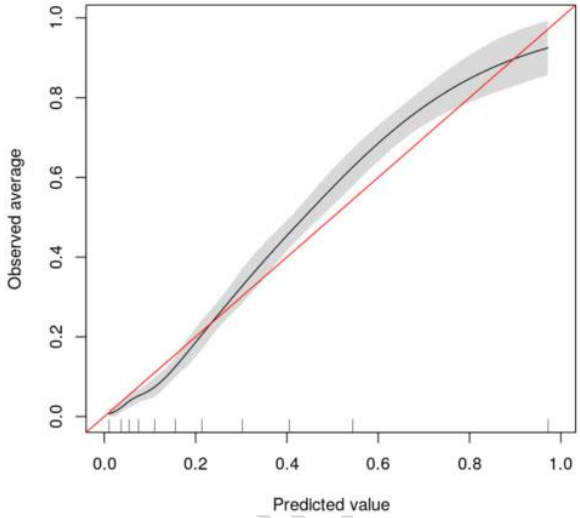

Fig.11: Calibration plot for binary prediction of "low" vs "higher" insulin users

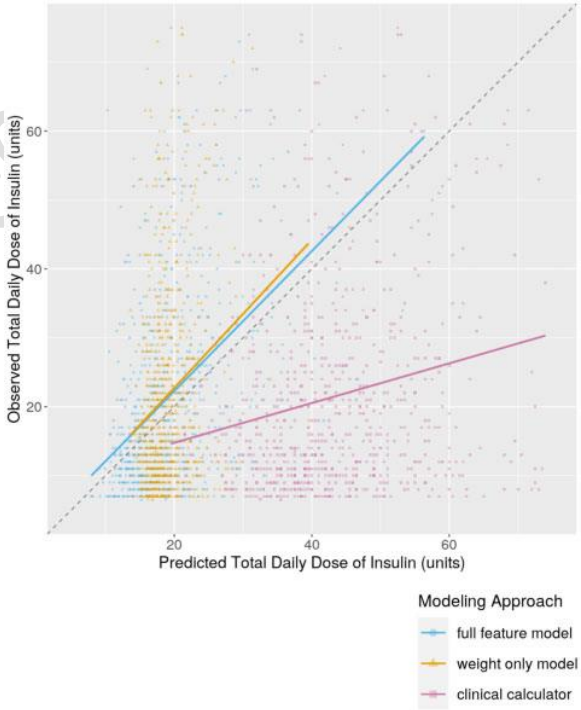

Fig.12: Plot of observed vs predicted total daily dose for all 3 modeling approaches

6. CONCLUSION

A machine learning approach can predict higher vs low insulin requirements among hospitalized patients with better discrimination than standard weight-based methods. Prediction of the initial daily insulin dosing with an ensemble learning method is more accurate compared with the current practice recommendations.

Challenges remain due to wide variability of patient response and narrow therapeutic window of insulin, but more accurate initial point-value TDD estimation can provide an improved dosing anchor for clinical decision making to improve inpatient glucose control.

7. FUTURE SCOPE

Additional studies shall be needed to the test of the real-time effectiveness of a informatics alert that derived from the prediction model in the reducing the incidence of this potentially serious adverse event.

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