SUPPLEMENTAL MATERIAL

Mortazavi: Analysis of Machine Learning Techniques for Heart Failure Readmissions

Supplemental Methods

Data Set Creation

Variables

This section details the creation of the features, the alignment of particular features, and the missing features. In particular, **Table S1** shows the list of all baseline variables collected in the Tele-HF trial. Removing Patient ID, the 236 remaining variables each had a duplicate binary variable created to indicate whether that value was missing or not (e.g., AGE_MISSING would be a binary variable with "yes" if the age was missing for that given patient and "no" otherwise). *Data Alignment*

The values in the variables are of three types, either binary, continuous, or categorical. However, due to the combination of multiple questionnaire types, the values assigned to the binary and categorical answers do not match. For example, one categorical value may have a numeric range from 1 to 5 where 1 is the worst answer and 5 is the best. The very next question may have five options as well but order them 0 to 4 where 4 is the worst. As a result, before any algorithms were run, all of the variables were ordered to increase as the answer improved (aligning the intensities as much as possible). The worst answer was given a value of 1 and the best answer would go up from there, 5 in most cases but up to 7 or 8 in many. Thus, the missing values would result in 0 being assigned. In this case the missing value provides no weight to the machine learning algorithm and can be considered either its own category or aligned with a truly negative response. This was chosen to integrate well with future endeavors on the telemonitoring data where the hypothesis to be tested is that missing data correlates strongly with negative responses and adverse outcomes.

Predictive Methods

Setting up the Outcome

Before we discuss the algorithms in further detail we should further outline how we arrived at the conclusion that we should weight our readmission cases heavily (equal to the proportion of not-readmitted vs. readmitted cases) versus the many other possibilities run in the 30-day prediction case (since the 180-day case had a roughly equal number of readmits to nonreadmits). We ran the following iterations of dealing with class imbalance. We first applied all the algorithms with no weighting and found that the probability of being predicted as a readmit was quite low. In order to balance the sets, we tried a number of techniques. We downsampled the non-readmit cases to be equal to the number of readmit cases in the training set, but found that the number of training samples was simply too small to create an effective model. We then upsample the readmitted cases to be equal to the number of non-readmit cases. This improved some of the algorithms and not all. The final approach we took was to vary our weighting of the readmit cases versus the non-readmit cases. Comparing the results of no weighting, downsampling, and upsampling, we observed that the weights setting the two sets to roughly equal seemed to be the best (which it was). To further confirm this observation, we varied the weight across a range from no weighting to twice as strong as the proportion of non-readmits to readmits. The rest of the methods described were run for each of these cases but the final outputs presented in the paper concern only the weighted examples.

Logistic Regression (LR) Comparisons

Three different LR models were built in order to validate the strength of the model presented in the main text, as well as to validate its use as a comparative technique to the machine learning (ML) models built. The first such model, based on $GLMNET¹$, was originally used for LR with Lasso regularization for feature selection, but the cross-validated LR in this model deemed no variables worthy of including in the final model so it produced a C-statistic of 0.5 since the only feature in the model was the intercept.

The second such model used the 236 Tele-HF variables and computed a forward, stepwise selection based upon the likelihood ratio of each variable. Forward selection was chosen because in certain high-dimensional datasets, the results are actually considered closer to the optimal solution than a Lasso regularization as in $GLMNET$ ². The method was run until no variable's likelihood had a p-value < 0.01. This technique produced a model, in 100 bootstrapped iterations, with a mean C-statistic of 0.524 with a 95% confidence interval over the 100 iterations of (0.518-0.529). Further, the model selected on average only 4.79 (95% CI: 4.5-5.1) variables. These variables selected were different in each iteration, with 80 of the 236 variables being selected across the 100 iterations. The variables selected are listed in **Table S2**. Note that the frequently-selected variables do not match those from Krumholz et al., indicating their valuation of variable importance results in the selection of more appropriate predictors**.**

The third such model used the full 472 variables created for this paper, including the dummy missing variables. Features were forward-selected similarly, and the method produced a C-statistic of 0.518 (0.512-0.524) with on average 5.53 (5.2-5.9) variables. Incidentally, this method selected 85 of the 472 variables, none of which were the missing dummy variables. These variables served only to affect the likelihood calculations and selections of the variables considered in the second method above, and increasing the number of variables beyond 5 actually lowered the C-statistic. As a result, the method chosen in the main text, based upon a prior study that comprehensively reviewed and evaluated the predictive capabilities of each variable in the Tele-HF dataset, produces the best and fairest comparison technique for the work.

Inputs and Outputs to Each Method

This section will cover in greater detail the machine learning algorithms considered and how they were coded in R for replication. SAS was used (proc logistic) to model the logistic regression as explained in the main text. The remainder of the techniques were coded in R.

The first ML technique, Poisson Regression¹, uses the input data as well as the total number of readmissions to create a predictive model based upon the propensity to be readmitted. This technique is classically used to predict a range of counts (e.g., the number of readmission events) it can also be used for comparing the binary case of readmitted/not readmitted, has a built in feature ordering and selection technique, and outputs the variables associated with the predictive model along with a propensity value for prediction. This value is given to the pROC package along with the ground truth labels to determine the ROC curve and area under the curve estimate.³

The second technique, Random Forests⁴ (RF), uses a series of decision trees on the input data to predict a final outcome by considering the result of each decision tree. The decision trees can be trained to output a binary decision or a prediction on the range of readmissions. Further, the ordering of features in the trees gives a selection of the most important features used for prediction. Finally, RF can be trained using the number of readmissions or the binary label of readmitted/not readmitted and can output probabilities of a binary prediction or a multiclass prediction (e.g., probability of each particular number of readmissions). For each of the test cases we had RF output the probabilities of being within each class. For the binary readmission case, the probability of being in class 1 (readmitted) was used for pROC calculations. For the counts of readmissions, we are given a matrix of probabilities where each column indicates each count, namely, 0 for no readmissions, 1 for 1 readmission, 2 for 2 readmissions and so on. We tested a combination of factors to add probabilities for a final 0 or 1 prediction. We tried the final 0 prediction probability being only the column associated with class 0. We then added the probability of being in class 1 with class 0 and called this a probability of not being readmitted, and so forth through all of the probabilities. When being fed into LR or support vector machines (SVM), it was these matrix of probabilities that were supplied as inputs. The results presented in the paper indicate the best form of this approach, where class 0 was considered no readmissions and the probabilities of all the other classes were added together to form the probability of being readmitted.

The third technique, that also contains a form of feature ranking, is Boosting. Boosting attempts to take a series of weak classifiers (e.g., tree classifiers based upon a single feature) that only classify pieces of the data well, and re-weigh them to develop an overall strong classifier. This iterative technique then builds a strong classifier as a weighted linear combination of the results of these weak classifiers, to output a binary outcome. We used the ADA package⁵ to test this method. This package has the flexibility of providing two loss functions, exponential and logistic, as well as the different kind of boosting techniques, discrete (also known as AdaBoost), real (for RealBoost), and gentle (for GentleBoost). The results presented in the paper were a summary of the best form of Boosting calculated by the algorithms.

The final ML technique considered is the SVM, implemented in R by the package e1071, of which the SVM implementation is known as $LibSVM⁶$. An SVM is a supervised learning model that leverages higher dimensional spaces to attempt to determine separation between the classes being trained. Unlike the previous methods, however, a feature selection algorithm must be run prior to the SVM to select the most relevant features. Such selection algorithms can be take many forms, and in this work, will be provided by RF, where the output from the RF models (the matrix of probabilities) will serve as the inputs to the SVM. Both linear and radial basis function kernels (RBF) were used but in each case the RBF algorithm outperformed the linear kernel. In some cases, the linear kernel was unable to converge on a solution in the given number of iterations.

Again, in all cases, instead of looking at a final response output, we looked at the probabilities of being readmitted generated by the algorithm, then supplied that to the pROC package to vary thresholds of readmitted/not readmitted and generate an ROC curve for us.

Using RF with Other Methods

RF is a method that is well-suited to a dataset of high dimensionality with a number of mixed types.⁷ RFs build decision trees where each node is split by a single chosen variable. This variable is selected by using out-of-bag estimates and bootstrapping to measure error, correlation

to other variables, and strength of prediction, to pick the best variables as well as ensure the model does not overfit.⁷ For this reason, RFs are often used in situations with a high-dimensional, varied dataset, to serve as a feature selection technique for other models as well as its own model.⁸⁻¹⁰ For this reason, this method is often used to select features, with the top importance features used to train methods such as SVM.

This work, similarly, leverages the ability of the RF method to evaluate a large set of variables and develop a predictive model without overfitting. However, rather than taking the selected variables, which might be of different types (e.g. continuous and categorical), RF can produce the probability of multiple events. For example, rather than have a binary yes/no prediction of readmission, RF can create a regression for the number of readmissions (e.g. 0-12) and provide a probability of each readmission count. These probabilities (13 of them in this case), are then provided as inputs to SVM and LR, methods that are at risk of overfitting if all the variables were to be provided to them. Thus, the hierarchical models created avoid overfitting by leveraging RFs, which avoid overfitting by using an internal bootstrapping and out-of-bag errors to ensure this. Further, the 100 bootstrapped iterations and the accuracy produced help verify that this is the case experimentally.

Creating Deciles of Risk

Similar to the ROC creation, each iteration of responses was also split into deciles using the R quantile function. Each iteration the boundary values from the predicted responses are taken for the deciles and a mean boundary value plus 95% confidence intervals around those boundaries are calculated. The total set of responses are also then combined and split into deciles to show the fraction of times correct across the cross-validated samples. We verified that the decile boundaries, created by the entire list of responses, falls within the 95% confidence interval calculated by each method for its particular range of responses. These were then used to give the observed readmission rates as detailed in the manuscript and results. **Table S3** gives an example of this for 30-day all-cause readmissions and the boundaries presented by RF.

Cohort Results

For the additional patients eliminated from the analysis because they died before being readmitted, we evaluated characteristics versus the cohort used for training. The analytic sample did not differ significantly from those who were excluded for various reasons (**Table S4**). Further, as the study excluded a large number of the original 1653 participants, we have listed the differences between the included cohort (n=1004) and excluded cohort (n=649) (**Table S5**). While many of the values are similar it might be interesting to further analyze their differences in future work. Finally, for the included patients, the percent missing for each variable is plotted in **Figure S1**. The complete missing information can be found in **Table S6.** In particular, the high rates of missing values for a large number of variables seems to be in large part as a result of incomplete questionnaires leading to summary scores that could not be calculated. While no individual patient within the cohort selected has a large rate of missing data, it does seem that the variables missing are consistent across all of the patients, which improves the likelihood that imputation is not causing a large effect on the outcome.

SUPPLEMENTAL REFERENCES

- 1. Friedman J, Hastie T and Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *Journal of statistical software*. 2010;33:1.
- 2. Zhang T. On the consistency of feature selection using greedy least squares regression. *J Mach Learn Res*. 2009;10:555-568.
- 3. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J-C and Müller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12:1.
- 4. Liaw A and Wiener M. Classification and regression by randomForest. *R news*. 2002;2:18-22.
- 5. Culp M, Johnson K and Michailidis G. ada: An r package for stochastic boosting. *J Stat Softw*. 2006;17:9.
- 6. Chang C-C and Lin C-J. LIBSVM: a library for support vector machines. *ACM Transactions on Intelligent Systems and Technology (TIST)*. 2011;2:27.
- 7. Breiman L. Random forests. *Mach Learn*. 2001;45:5-32.
- 8. Hapfelmeier A and Ulm K. A new variable selection approach using random forests. *Comput Stat Data Anal*. 2013;60:50-69.
- 9. Genuer R, Poggi J-M and Tuleau-Malot C. Variable selection using random forests. *Pattern Recognition Letters*. 2010;31:2225-2236.
- 10. Verikas A, Gelzinis A and Bacauskiene M. Mining data with random forests: a survey and results of new tests. *Pattern Recognition*. 2011;44:330-349.

SUPPLEMENTAL FIGURE LEGEND

Figure S1. Variable missing rates for all variables with a rate of missing greater than 3% across the 1004 patient cohort.

SUPPLEMENTAL TABLES

Table S1. The 236 Features Used in the Tele-HF Analysis

Laboratory Values and Physical Exams

Feature	Number of Times Selected
ALBUMIN	$\mathbf{1}$
METASTATIC_TUMOR_	5
CORONARY_ARTERY_	3
KCCQ_BOTHER_	3
ALONE	$\mathbf{1}$
$WARE_1$	$\mathbf{1}$
PHQ9_INTEREST_	3
CHRONIC_RENAL_FAILURE_	1
DEPENDENT_	$\mathbf{1}$
WARE_EXPLAIN_	1
BLOOD_UREA_NITROGEN_	6
KCCQ_EFFICACY_	6
KCCQ DISCOURAGED	$\mathbf{1}$
PATIENT_SCALE_SOURCE_	1
WARE	$\overline{3}$
DIABETES	$\mathbf{1}$
DOCYRS	$\overline{2}$
$RACE_6$	$\mathbf{1}$
PHQ9_	1
CONNECTIVE_TISSUE_	$\overline{2}$
KCCQ_QUALITY_	$\mathbf{1}$
KCCQ_STAIRS_	$\overline{4}$
KCCQ_UNDERSTAND_	3

Table S2. Variables Selected in the Forward, Stepwise Selection Method for LR

- ENROLL_LANGUAGE 2
- KCCQ_FREQUENCY 3
- WARE_EMERGENCY_ 1
- CREATININE_ 2
- JVD_MEASURE_ 1
- BURDEN 17
- RELIGION 9
- MORISKY_FORGOT 4
- KCCQ_JOGGING 12
- KCCQ BURDEN 5
- ESSI_CHORES_6
- REALM_DIRECTED_1
- MEDCOSTS 2
- KCCQ_VISITING_ 2
- CHRONIC_PULMONARY_ 5
- ADMITTED 28
- SCHFI³
- REALM_OSTEOPOROSIS 1
- KCCQ SHORTNESSBOTHER 2
- KCCQ_STABILITY_ 1
- KCCQ WORK 4
- FINANCIAL 1
- DISEASE_MANAGEMENT_ 1
- WARE_SPECIALIST 2
- PAYOR 8 2

- GFR_ 2
- KCCQ_SWELLING_ 24
- RACE 3 6
- $Rx1_0$ 1
- INSURANCE_ 2
- PSS_DIFFICULTY_ 1
- PAYOR 6 2
- KCCQ_SUMMARY_ 5
- OXYGEN_ 1
- Rx2_0_ 1
- DOCMOS_ 1
- HEALTH_ 2
- EDUCATION_ 1
- PEPTIC_ULCER_ 1
- LIVER_DISEASE_RATING_ 1
- KCCQ_HOBBIES_ 1
- KCCQ_YARDWORK_ 5
- HF_HOSP 13
- KCCQ_PHYSICAL_ 4
- KCCQ SYMPSCORE 1
- SCHFI_HEALTH_ 1
- TUMOR_ 2
- VISITEDQT_ 2
- KCCQ_FATIGUE_ 2

Deciles	Overall Boundary	Mean (95% CI)
1	0.392	$0.393(0.390 - 0.396)$
$\overline{2}$	0.418	$0.420(0.417 - 0.423)$
3	0.438	$0.439(0.436 - 0.442)$
$\overline{4}$	0.456	$0.456(0.453 - 0.459)$
5	0.472	$0.472(0.469 - 0.475)$
6	0.488	$0.487(0.484 - 0.490)$
$\overline{7}$	0.504	$0.503(0.500-0.506)$
8	0.524	$0.522(0.519 - 0.525)$
9	0.550	$0.548(0.545-0.551)$
10	1.00	$1.00(1.00-1.00)$

Table S3. Deciles and Confidence Intervals for 30-day All-Cause Readmission Responses from RF

Characteristic	Excluded	Included
	N(%)	N(%)
$\mathbf N$	27(100.0)	977 (100.0)
Median age (SD)	66.5 (12.2)	62(15.7)
Females	12(44.4)	403 (41.2)
Race		
White	16(59.3)	491 (50.3)
African American	8(29.6)	385 (39.4)
Other	3(11.1)	101(10.3)
New York Heart		
Association		
Class I	2(7.41)	54(5.5)
Class II	15(55.6)	500 (51.2)
Class III	8(29.6)	347 (35.5)
Class IV	1(3.70)	57(5.8)
Missing	1(3.70)	19(2.0)
Medical History		
LVEF† $\% < 40$	19(70.4)	668 (68.4)
Hypertension	19 (70.4)	752 (77.0)
Diabetes	11(40.7)	439 (44.9)
Myocardial Infarction	7(25.9)	250 (25.6)
Stroke	4(14.8)	92 (9.4)
Ischemic	7(25.9)	228 (23.3)

¹⁸⁰⁻Day

Cardiomyopathy

Clinical Values

(Mean/SD)

*All values in tables are mean (standard deviation) unless noted.

†LVEF: Left Ventricular Ejection Fraction.

Table S5. Excluded Patient Characteristics

Medical History

*All values are mean (standard deviation) unless noted.

†LVEF, Left Ventricular Ejection Fraction

Table S6. Percentage of Missing Per Variable from the 236 Variables in the Cohort of 1004 Patients

SUPPLEMENTAL FIGURE

Figure S1

