IMPROVING OUTCOME PREDICTIONS FOR PATIENTS RECEIVING

MECHANICAL CIRCULATORY SUPPORT BY OPTIMIZING IMPUTATION OF MISSING VALUES

A PREPRINT

|  |  |
| --- | --- |
| Byron C. Jaeger ∗  Department of Biostatistics  University of Alabama at Birmingham  Birmingham, AL  bcjaeger@uab.edu | Ryan Cantor, PhD  University of Alabama at Birmingham Birmingham, AL |
| Venkata Sthanam, MS  University of Alabama at Birmingham Birmingham, AL | Rongbing Xie, DrPH  University of Alabama at Birmingham Birmingham, AL |
| James K. Kirklin, MD  University of Alabama at Birmingham Birmingham, AL | Ramaraju Rudraraju, PhD  University of Alabama at Birmingham  Birmingham, AL  ramaraju@uab.edu |

November 9, 2020

ABSTRACT

Background Risk prediction models play an important role in clinical decision making. When developing risk prediction models, practitioners often impute missing values to the mean. We evaluated the impact of applying other strategies to impute missing values on the prognostic accuracy of downstream risk prediction models, i.e., models fitted to the imputed data. A secondary objective was to compare the accuracy of imputation methods based on artificially induced missing values. To complete these objectives, we used data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).

Methods and Results We applied twelve imputation strategies in combination with two different modeling strategies for mortality and transplant risk prediction following surgery to receive mechanical circulatory support. Model performance was evaluated using Monte-Carlo cross validation and measured based on outcomes 6-months following surgery using the scaled Brier score, concordance index, and calibration error. We used Bayesian hierarchical models to compare model performance. Multiple imputation with random forests emerged as a robust strategy to impute missing values, increasing model concordance by 0.003 (25th, 75th percentile: 0.008, 0.052) compared with imputation to the mean for mortality risk prediction using a downstream proportional hazards model. The posterior probability that single and multiple imputation using random forests would improve concordance versus mean imputation was 0.482 and 0.962, respectively.

Conclusion Selecting an optimal strategy to impute missing values and applying multiple imputation can improve the prognostic accuracy of downstream risk prediction models.

*K*eywords Missing Data · INTERMACS · imputation · heart failure · mortality · risk prediction

∗Source code available at <https://github.com/bcjaeger/INTERMACS-missing-data>

# 1 Introduction

1. Heart disease is a leading cause of death in the United States. Heart failure, a primary component of heart disease, affects
2. over 6 million Americans, and for ~10% of these patients medical management is no longer effective [1, 2]. Mechanical
3. circulatory support (MCS) is a surgical intervention in which a mechanical device is implanted in parallel to the heart to
4. improve circulation [3]. Typically, MCS is used while a patient waits for a heart transplant (bridge-to-transplant) or in
5. some cases as an alternative to transplant (destination therapy) [4]. Over 250,000 patients could benefit from MCS [5].
6. However, less than 4,000 new patients receive a long-term MCS device each year, with widely heterogeneous outcomes
7. [6]. The 2-year survival probability on MCS ranges from 61% for destination therapy to 78% for bridge-to-transplant
8. [3]. Reliable predictions of patient-specific risk to experience key outcomes such as mortality or transplant after 9 receiving MCS can help improve patient selection, inform the design of next generation pumps, and improve patient 10 care strategies.
9. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) was launched to improve
10. MCS patient outcomes through the collection of patient characteristics, medical events, and long terms outcomes
11. at a nation wide level. Currently, INTERMACS comprises over 20,000 patients who have received a MCS device.
12. As the largest registry for data on patients receiving MCS devices, INTERMACS has been leveraged to develop
13. numerous risk prediction models for mortality and other types of adverse events that may occur after receiving a device
14. [7, 8, 9, 10, 11, 12]. A critical step for developing risk prediction models is handling missing data, which is common in
15. a “real world” database that is not designed for the rigor of data completeness found in a clinical trial. While some 18 missing values are related to data entry error, others may relate to instability of a patient’s circulatory status at the time

19 of implant. For instance, hemodynamic laboratory values are missing for patients in whom invasive catheterizations 20 were not performed. Patients without invasive catheterizations may be too ill (unstable) to tolerate the procedure. 21 Instead, such patients may, after determination of basic hemodynamics, proceed directly to device placement.

22 The primary aim of this article is to quantify how much the prognostic value of a risk prediction model developed from 23 the INTERMACS registry depends on the strategy that was applied to impute missing data prior to developing the

1. model. A secondary aim is to measure imputation accuracy of each strategy by introducing varying levels of artificial
2. missing data and then imputing it. Because imputation to the mean has been a standard method for multiple annual
3. summaries of the INTERMACS data, we measure the potential improvement in prognostic value of a risk prediction
4. model when other strategies are applied to impute missing data *instead of imputation to the mean*. The over-arching 28 aim is to clarify which imputation strategies are most likely to improve risk prediction (and by extension, quality of 29 care) for patients who receive MCS devices. This investigation can directly inform future analyses of INTERMACS

30 data and provide evidence quantifying the benefit of imputing missing data with sound methodology.

# 2 Methods

1. 2.1 INTERMACS Registry
2. INTERMACS is a North American observational registry for patients receiving MCS devices that began as a partnership
3. between the National Heart, Lung, and Blood Institute, US Food and Drug Administration, the Centers for Medicaid 5 and Medicare Services, industry, and individual hospitals with the mission of improving MCS outcomes. In 2018, 6 INTERMACS became an official Society of Thoracic Surgeons database.
4. The current analysis was conducted using publicly available data provided by the National Heart, Lung, and Blood
5. Institute (see [https://biolincc.nhlbi.nih.gov/studies/intermacs/)](https://biolincc.nhlbi.nih.gov/studies/intermacs/). We included a contemporary cohort of 9 14,738 patients who received continuous flow LVAD from 2012-2017. This is a secondary analysis of de-identified data

10 obtained from the National Heart Lung and Blood Institute. Primary data collection is approved through University of 11 Alabama Institutional Review Board and at individual sites.

1. 2.2 Outcomes and Predictors
2. Patient follow-up begins after implantation of a durable, long term MCS device and continues while the device is
3. in place. Registry endpoints include death on a device, heart transplantation, or cessation of support (for recovery 15 and non-recovery reasons). Mortality and transplant after MCS were the primary outcomes for the current study. As
4. there were only 310 cessation of support events, we did not analyze this outcome. For mortality and transplant risk
5. prediction models, we applied cause-specific analysis to account for competing risks. For example, in risk prediction
6. models for mortality, patients were censored at time of loss to follow-up, transplant, or cessation of support, whichever
7. occurred first. INTERMACS collects pre-implant data on patient characteristics, medical status, and laboratory values.
8. INTERMACS also collects follow-up data at regularly scheduled visits and at occurrence of adverse events such as 21 re-hospitalization. For the current analysis, all pre-implant variables were considered as potential predictors.
9. 2.3 Statistical Inference and Learning with Missing data
10. Statistical Inference To conduct statistical inference in the context of missing data setting, analysts often create
11. multiple imputed datasets, replicate an analysis in each of them, and then pool their results to obtain valid test statistics
12. for hypothesis testing [13]. Imputation strategies that create a single imputed dataset (*e.g.,* imputation to the mean)
13. have been shown to increase type I errors (*i.e.,* rejecting a true null hypothesis) for inferential statistics by artificially
14. reducing the variance of observed data and ignoring the uncertainty attributed to missing values [14]. To ensure valid
15. inference, imputation models should leverage outcome variables to predict missing predictors [15]. When very few 29 data are missing, analysts may apply listwise deletion, *i.e.,* removing any observation with at least one missing value.

30 However, listwise deletion can easily lead to biased inference [16].

Statistical Learning In the presence of missing data, the goal of supervised statistical learning is to develop a prediction function for an outcome variable that accurately generalizes to testing data, which may or may not contain missing values [17]. Because testing data may contain missing values, listwise deletion is not a feasible strategy for statistical learning tasks. In contrast to statistical inference, strategies that create a single imputed dataset are often

1. used for statistical learning [18]. Previous work has emphasized the importance of imputation strategies with greater
2. accuracy, suggesting that more accurate imputation strategies lead to better performance of downstream models (*i.e.,*
3. models fitted to the imputed data) [19]. Others have shown that imputation to the mean, model-based imputation, and
4. multiple imputation can provide Bayes-optimal prediction models provided certain assumptions are true, but these 9 assumptions are difficult to validate in applied settings [20].
5. Using outcomes during imputation The outcome variable should be used to impute predictor values for statistical
6. inference, but using outcome variables for this purpose in supervised learning can have unintended consequences in
7. model implementation. For instance, suppose we seek to predict an outcome *Y* for a patient in the clinical setting. If
8. the patient is missing information for a predictor *X* and our model’s strategy to impute missing values of *X* leverages
9. the observed value of *Y* , how should we impute *X*? If we do not already know *Y* , then we cannot impute *X* and hence
10. cannot generate a valid prediction. On the other hand, if we already know *Y* , then we do not need to predict it. Due to
11. these practical considerations and because INTERMACS is often leveraged to create prediction models for clinical 17 practice [21], we did not leverage outcome variables to impute missing values of predictors in the current analysis.
12. 2.4 Missing Data Strategies
13. Single and multiple imputation Several of the imputation methods we considered allowed for creation of single or
14. multiple imputed datasets. For downstream models fitted to multiple sets of imputed data, we applied the modeling
15. technique to each imputed training set, separately, and then used a pooling technique to generate a single set of 22 predictions based on multiple imputed testing data. Specifically, we created 10 imputed training and testing sets, then

23 applied a modeling procedure to each imputed training set and computed model predictions on the corresponding 24 imputed testing set, which led to 10 sets of predictions. To aggregate these predictions, we computed the median for

25 each patient. Informal experiments where the mean was used instead of the median to aggregate predictions showed 26 little or no difference in the model’s prediction accuracy.

1. Imputation to the mean Imputing data to the mean involves three steps. First, numeric and nominal variables
2. are identified. Second, for each numeric variable, the mean is computed and used to impute missing values in the
3. corresponding variable. Third, for each nominal variable, the mode is computed (because one cannot compute a mean
4. for categorical variables) and used to impute missing values in the corresponding variable. The computed means and 31 modes are then stored for future imputation of testing data. Because imputation to the mean is frequently used in

32 practice, we use it as a reference for comparison of all other strategies to impute missing values.

Bayesian Regression Imputation with Bayesian regression draws imputed values from the posterior distribution of model parameters, accounting for uncertainty in both model error and estimation [13]. Multiple imputation with chained equations (MICE), a well known technique for generating multiply imputed data [22, 14, 23]. In each iteration of MICE, each specified variable in the dataset is imputed using other variables in the dataset. These iterations are run 5 until convergence criteria have been met.

1. Predictive Mean Matching (PMM) PMM computes predicted values from a pre-specified model that treats one
2. incomplete column in the data, *X*, as a dependent variable. For each missing value in *X*, PMM identifies a set of
3. candidate donors based on distance in predicted values of *X* [24]. One donor is randomly drawn from the candidates,
4. and the observed value of the donor is taken to replace the missing value. When missing values were imputed using
5. PMM, we applied MICE to form multiple imputed datasets. For consistency with other approaches, we also generated a 11 single imputed dataset using PMM by randomly selecting one of the multiple datasets imputed.
6. K-Nearest-Neighbors (KNN) KNN imputation identifies *k* ‘similar’ observations (*i.e.,* neighbors) for each observa-
7. tion with a missing value in a given variable [25]. A donor value for the current missing value is generated by sampling
8. or aggregating the values from the *k* nearest neighbors. In the current analysis, we identified 10 nearest neighbors using
9. Gower’s distance [26]. When imputing a single dataset using KNN, we aggregated values from 10 nearest neighbors
10. using the median for numeric variables and the mode for categorical variables. When imputing multiple datasets using 17 KNN, we aggregated values from 2, 6, 11, 16, and 20 neighbors, separately, to create 5 imputed datasets.
11. Hot Deck Similar to KNN, hot deck imputation finds *k* similar observations for each observation with a missing
12. value in a given variable [27]. However, hot deck imputation uses a less computationally intensive approach, either 20 identifying neighbors at random or using a subset of variables to find similar observations. When imputing a single 21 dataset using hot deck imputation, we used a selection of 5 variables simultaneously to identify nearest neighbors. 22 When imputing multiple datasets using hot deck imputation, we used a separate numeric variable for each dataset.
13. Random forests Random forests grow an ensemble of de-correlated decision trees, where each tree is grown using a
14. bootstrapped replicate of the original training data [28, 29, 30, 31, 32, 33]. A particularly helpful feature of random 25 forests is their ability to estimate testing error by aggregating each decision tree’s prediction error on data outside of
15. their bootstrapped sample (*i.e.,* out-of-bag error). In the current analysis, we conduct MICE using one random forest to
16. impute each variable, separately. For each imputed dataset, we allowed random forests to be re-fitted until out-of-bag
17. error stabilized or a maximum number of iterations was completed. When imputing a single dataset, we used 250
18. trees per forest and a maximum of 10 iterations. When imputing multiple datasets, we used 50 trees per forest and 30 applied PMM using the random forest’s predicted values to impute missing data by sampling one value from a pool of 31 10 potential donors.

Missingness incorporated as an attribute (MIA) MIA is a technique that uses missing status as a predictor rather than explicitly imputing missing values [34, 35]. MIA adds another category to nominal variables: “Missing”. For numeric variables, MIA creates two columns: one where missing values are imputed with positive infinity and the other with negative infinity. Since PH models are not compatible with infinite values, we only use MIA in boosting models. 5 When a decision tree uses a finite cut-point to split a given numeric variable, it will assess the cut-point using both the

1. positive and negative infinite imputed columns, and utilize whichever column provides the best split of the current data.
2. This procedure translates to sending all missing values to the left or to the right when forming two new nodes of the 8 decision tree, using whichever direction results in a better split.
3. Assumptions Each missing data strategy poses different assumptions regarding the data and the mechanisms that
4. lead to missing values in the data. Imputation using Bayesian regression makes the same distributional assumptions as
5. the Bayesian models that are applied. The miceRanger algorithm does not make any formal distributional assumptions,
6. as random forests are non-parametric and can thus handle skewed and multi-modal data as well as categorical data that
7. are ordinal or non-ordinal. Hot deck and KNN imputation also do not make distributional assumptions, but implicitly
8. assume that a missing value for a given observation can be approximated by aggregating observed values from the 15 *k* most similar observations. PMM makes a similar implicit assumption, but is slightly more robust to skewed or
9. multi-modal data because imputed values are sampled directly from observed ones. MIA operates based on an implicit
10. assumption that missingness itself is informative. It is difficult to validate these assumptions in applied settings and also 18 likely that downstream models will perform poorly if an imputation technique’s assumptions are invalid.
11. 2.5 Evaluating Imputation Accuracy
12. Imputation accuracy was computed for each numerical and nominal variable, separately. Numeric variable imputation 21 accuracy was measured using a re-scaled mean-squared error:

MSE(current imputation method)

1 − *.*

MSE(imputation to the mean)

1. This score is greater than 0 if MSE(current imputation method) is smaller than MSE(imputation to the mean),
2. equal to 0 if the two MSEs are equal, and less than 0 if MSE(current imputation method) is greater than 24 MSE(imputation to the mean). Nominal variable imputation accuracy was measured using a re-scaled classification
3. accuracy:

Classification error(current imputation method)

1 − *.*

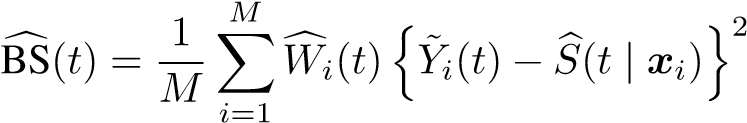
Classification error(imputation to the mean)

1. This score is greater than 0 if the classification error of the current imputation method is less than that of imputation to
2. the mean, equal to 0 if the two classification errors are equal, and less than 0 of the classification error of the current 28 imputation method is worse than imputation to the mean. These numeric and nominal scores are analogous to the more

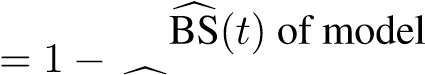
29 well known *R*2 and Kappa statistics, respectively, but are modified slightly in the current analysis so that imputation to

the mean will always have a score of 0. This modification makes it easier to compare the accuracy of each imputation strategy directly with that of imputation to the mean.

1. 2.6 Risk Prediction Models
2. We applied two modeling strategies after imputing missing values:
3. • Cox proportional hazards (PH) model with forward stepwise variable selection
4. • Gradient boosted decision trees (hereafter referred to as ‘boosting’)
5. A thorough description of stepwise variable selection and boosting can be found in Sections 6.1.2 and 8.2.2, respectively,
6. of *Introduction to Statistical Learning* [36]. Sir David Cox’s PH model is one of the most frequently applied methods
7. for the analysis of right-censored time-to-event outcomes [37]. According to the PH assumption, the effect of a unit
8. increase in a predictor is multiplicative with respect to a baseline hazard function. Boosting grows a sequence of 11 decision trees, each using information from the previous trees in an attempt to correct their errors [38, 39].
9. 2.7 Evaluation of Predictions
10. The Brier score The prognostic value of each risk prediction model was primarily assessed using the Brier score,
11. which depends on both the discrimination and calibration of predicted risk values [40, 41]. Let *Y*˜*i*(*t*) represent the
12. observed status of individual *i* at time *t >* 0 in a testing set of *M* observations. Suppose *Y*˜*i*(*t*) = 1 if there is an 16 observed event at or before *t* and *Y*˜*i*(*t*) = 0 otherwise. The Brier score is computed with

 *,* (1)

1. where, for the *ith* observation, is the estimated probability of survival at time *t* according to a given risk
2. prediction model, *xi* is the set of input values for predictor variables in the model, and is the inverse proportional 19 censoring weight at time *t* [42]. Thus, the Brier score is the mean squared difference between observed event status 20 and expected event status according to a RPE at time *t*. Throughout the current analysis, we set *t* = 6 months after 21 receiving MCS to focus on short term risk prediction. Models have been developed to simultaneously predict short term 22 and long term mortality risk after receiving MCS, but these are beyond the scope of the current study [43].
3. The scaled Brier score The Brier score is dependent on the rate of observed events, which can make it a difficult
4. metric to interpret. It is often more informative to scale the Brier score based on the Brier score of a naive model. More 25 specifically, for a given risk prediction model, the scaled Brier score is computed as

Scaled of model *.* BS(*t*) of naive model

As the Brier score for risk prediction is analogous to mean-squared error for prediction of a continuous outcome, the scaled Brier score is analogous to the *R*2 statistic. Similar to the *R*2 statistic, a scaled BSc(*t*) of 1.00 and 0.00 indicate a

1. perfect and worthless model, respectively. In our analyses, a Kaplan-Meier estimate based on the training data (*i.e.,* a
2. risk prediction model that did not use any predictor variables) provided the naive prediction. In the current analysis, we 5 multiply scaled Brier score values by 100 for ease of interpretation.
3. Discrimination and calibration The discrimination of a risk prediction model measures the probability that the
4. model will successfully identify which of two observations is at higher risk for the event of interest. We estimated
5. discrimination using a time-dependent concordance (C-) index that accounted for covariate-dependent censoring. A 9 C-index of 0.50 and 1.00 correspond to worthless and perfect discrimination, respectively. Similar to the scaled Brier

10 score, we multiply C-index values by 100 for ease of interpretation. Calibration slope plots measure a risk prediction 11 model’s absolute accuracy. We estimated calibration error by averaging the squared distance between expected and

1. observed event rates according to a calibration plot. Full description of these evaluation metrics are available [44, 45].
2. 2.8 Internal Validation via Monte-Carlo Cross-Validation (MCCV)
3. To assess the prognostic value of each missing data strategy, we internally validated a total of 23 modeling algorithm
4. based on combinations of imputation strategies and modeling strategies described in Sections 2.4 and 2.6. For
5. convenience, we use the term ‘modeling algorithm’ to denote the combination of a missing data strategy and a modeling
6. strategy (*e.g.,* imputation using mean/mode values followed by fitting the PH model with stepwise variable selection) 18 [46]. We conducted internal validation using 200 replicates of Monte-Carlo cross validation, a resampling technique for 19 internal validation.
7. Steps taken in each replicate In each replicate of Monte-Carlo cross validation, 50% of the available data were used
8. for model training and testing. All predictor variables with < 50% missing values were considered for imputation and
9. subsequent model development. Among these variables, artificial missingness (0%, 15%, or 30% additional missing
10. values) was induced based on patient age, with younger and older patients more likely to have missing data compared
11. to patients who were between 40 and 65 years of age. Prior to imputation, 50 predictor variables were selected using a 25 boosting model that quantified variable importance as the fractional contribution of each predictor to the model based 26 on the total gain attributed to using the predictor while growing decision trees. Imputation was conducted in the training
12. and testing sets, separately, for each imputation strategy. Although some imputation strategies (*e.g.,* KNN and random
13. forests) can impute data in the testing set using models fitted to the training set, others (*e.g.,* Bayesian regression, PMM,
14. and hot deck) cannot. Therefore, to ensure fair comparisons in our experiment, each imputation procedure imputed data
15. in the training set using models fitted to the training set and then imputed data in the testing set using models fitted to 31 the testing set. After imputation, Cox PH and boosting models were applied to each imputed dataset, separately. Last,

32 model predictions for death and transplant were computed at 6 months following MCS surgery.

Bayesian analysis of model performance To determine whether any of the imputation methods described above had improved upon imputation to the mean, we applied Bayesian hierarchical models to analyze differences in scaled Brier

1. score [47]. This strategy provides a flexible framework to conduct hypothesis testing and also accounts for correlation
2. occurring within each replicate of Monte-Carlo cross validation. Specifically, within each replicate of Monte-Carlo
3. cross validation, the performance of different modeling algorithms are correlated because they are trained and tested 6 using the same data.
4. 2.9 Statistical analysis
5. Participant characteristics were tabulated for the overall population and stratified by event status. Continuous and
6. categorical variables were summarized as mean (standard deviation) and percent, respectively. The number and
7. proportion of missing values were also tabulated for the overall population and stratified by event status. Missing
8. data patterns were visualized for the overall population using an UpSet plot [48]. All of the proceeding analyses were
9. conducted using resampling results from Monte-Carlo cross validation. Imputation accuracy was aggregated for all
10. numeric and nominal variables to create two overall scores for each imputed dataset. For imputation methods that
11. created multiple datasets, scores were aggregated over each dataset to provide a single summary score. The distribution 15 (*i.e.,* 25th, 50th, and 75th percentile) of the scaled Brier score was estimated for each modeling algorithm.
12. We split our results from Monte-carlo cross validation into four datasets based on outcome (mortality or transplant)
13. and modeling procedure (Cox PH or boosting). For each dataset, we fit one hierarchical Bayesian model where the
14. dependent variable was scaled Brier score and independent variables included the imputation strategy applied and the
15. amount of artificially missing data (0%, 15%, or 30%) induced before imputation. With each model, we estimated the 20 difference in scaled Brier score of downstream models when random forests, Bayesian regression, PMM, hot deck, 21 MIA, or KNN imputation were applied to impute missing values instead of imputation to the mean.
16. 2.10 Computational Details
17. SAS software (version 9.4) and Python (version 3.8.2) were used to create analytic data for the current study [49, 50].
18. Base R (version 4.0.3) was used in combination with a number of open-source R packages (*e.g.,* drake, tidyverse, 25 naniar, table.glue, mice, miceRanger, and others) to conduct our analysis [51, 52, 53, 54, 55, 56, 57, 58, 59, 60,
19. 61]. Our R code is available on GitHub (see [https://github.com/bcjaeger/INTERMACS-missing-data)](https://github.com/bcjaeger/INTERMACS-missing-data) [62].
20. We used Cheaha, a high performance computing cluster at University of Alabama at Birmingham, to perform the 200 28 Monte-Carlo cross validation runs [63].

# 29 3 Results

1. Patient Characteristics During the first 6 months after receiving MCS, the number (% of overall population) of
2. deaths, transplants, and loss-to-follow-up events was 1,897 (13%), 1,067 (7.2%), and 981 (6.7%), respectively. The mean (standard deviation) age of patients was 57 (13) years, 66% of patients identified as white and 79% were male (Table 1).
3. Missing data Many predictor variables exhibited similar proportions of missing values in different outcome groups
4. (Table 2). However, the number (percent) of missing values for surgery time was an exception, with 6,125 (41.6%) in
5. the overall population, 2,246 (53.4%) among patients who died, and 1,713 (27.2%) among patients who were censored. 6 Additionally, missing values for surgery time were frequently accompanied by missing values for CV pressure (Figure 7 1).
6. Imputation accuracy Single imputation strategies were more accurate than their counterparts using multiple imputa-
7. tion in 8 out of 10 comparisons of nominal scores and 10 out of 10 comparisons of numeric scores (Table 3). When an
8. additional 15% of data were missing, single imputation KNN obtained the highest nominal accuracy (score: +0.02, 95%
9. CI -0.05, 0.15) and single imputation with random forests obtained the highest numeric accuracy (score: +0.05, 95% CI
10. 0.03, 0.08). When an additional 30% of data were missing, imputation to the mean obtained the highest numeric and 13 nominal scores.
11. 3.1 Scaled Brier score
12. Mortality risk prediction When no additional data were amputed and imputation to the mean was applied before
13. fitting risk prediction models, the median (25th, 75th percentile) scaled Brier score was 6.09 (5.71, 6.54) for Cox PH and
14. 7.27 (6.83, 7.77) for boosting models (Table 4; top panel). Multiple imputation strategies universally obtained higher 18 scaled Brier scores versus their single imputation counterparts. Multiple imputation using random forests provided the 19 highest scaled Brier score compared to other strategies, leading to a median (25th, 75th percentile) increase in the scaled

20 Brier score of 0.34 (0.12, 0.54) for Cox PH and 0.34 (0.14, 0.58) for boosting models. These performance increments 21 improved when an aditional 15% and 30% of data were amputed (Table 4; middle and bottom panel).

1. Transplant risk prediction When no additional data were amputed and imputation to the mean was applied before
2. fitting risk prediction models, the median (25th, 75th percentile) scaled Brier score was 9.35 (8.80, 9.71) for Cox PH and
3. 9.00 (8.55, 9.41) for boosting models (Table 5; top panel). For Cox PH models, imputation to the mean provided the
4. lowest scaled Brier score, and random forest imputation led to a median (25th, 75th percentile) increase of 0.13 (0.03,
5. 0.29) versus imputation to the mean. For boosting models, surprisingly, imputation to the mean provided a higher scaled
6. Brier score than all imputation methods except for multiple imputation using Bayesian regression. When an additional 28 15% and 30% of data were amputed, the performance increments corresponding to the use of multiple imputation

29 increased for both Cox PH and boosting models (Table 5; middle and bottom panel).

3.2 Discrimination and calibration

1. Mortality risk prediction Regardless of how much additional data were amputed, boosting models obtained higher
2. median C-indices than PH models for prediction of 6-month mortality risk (Table 6). In addition, all models that
3. used multiple imputation consistently obtained higher median C-indices compared to their counterparts using single
4. imputation. When 0 and 15% additional data were amputed, median calibration error was lower for PH models
5. compared to boosting models, but boosting models obtained lower median calibration error when 30% additional data
6. were amputed (Table 7). Almost all imputation strategies provided lower median calibration error compared with 8 imputation to the mean.
7. Transplant risk prediction For all amounts of additional data amputed, PH models obtained higher median C-indices
8. than boosting models for prediction of 6-month transplant risk (Table 8). Similar to mortality risk prediction, multiple 11 imputation strategies generally provided higher C-indices than their counterparts using single imputation strategy. For
9. boosting models, MIA provided higher C-indices compared to all other single imputation strategies and had similar or
10. superior performance compared to several multiple imputation strategies. Differences in calibration error were minor
11. when no additional missing data were amputed (Table 9). When an additional 30% of data were amputed, boosting 15 models using MIA obtained lower calibration error than any other strategy.
12. 3.3 Bayesian analysis of model performance
13. Adjusting for the amount of additional missing data amputed and the outcome variable, the posterior probability that an
14. imputation strategy would improve the scaled Brier score of a downstream model relative to imputation to the mean was
15. maximized by using multiple imputation with random forests (probability of improvement: 1.000; Figure 2). Similarly,
16. multiple imputation using random forests was estimated to have the highest posterior probability of improving the
17. C-index in comparison to using imputation to the mean (probability of improvement: 1.000; Figure 3). However, the
18. estimated posterior probability of a reduction in calibration was 1 when using either single or multiple imputation 23 with random forests compared with imputation to the mean (Figure 4). Although imputation using random forest was
19. estimated to be the best overall option, there was moderate to strong evidence that MIA and each multiple imputation
20. strategy we applied would improve prognostic accuracy of downstream models compared with imputation to the mean.

# 26 4 Discussion

1. In this article, we leveraged INTERMACS registry data to evaluate how the use of different imputation strategies prior
2. to fitting a risk prediction model would impact the external prognostic accuracy of the model. External prognostic
3. accuracy was measured at 6 months after receiving MCS, and the primary measure of accuracy was the scaled Brier
4. score. We evaluated the performance of 12 imputation strategies in a broad range of settings by varying (1) the amount 31 of additional missing data amputed prior to performing imputation, (2) the type of risk prediction model applied after

32 imputation, and (3) the outcome variable for the risk prediction model. Our resampling experiment indicated that conducting multiple imputation has a high likelihood of increasing the downstream scaled Brier score and C-index of 2 risk prediction models compared with imputation to the mean. Additionally, multiple imputation with random forests

3 emerged as the imputation strategy that maximized the probability of developing a more prognostic model compared 4 with imputation to the mean.

1. In previous studies involving the INTERMACS data registry, imputation to the mean has been applied prior to developing
2. a mortality risk prediction model [7, 8, 9, 10, 11, 12]. An interesting recent study indicates that imputation to the mean
3. can provide an asymptotically consistent prediction model, given the prediction model is flexible and non-linear [20].
4. However, theoretical results for finite samples have not yet been established. Our results provide relevant data for the 9 finite sample case, suggesting that using imputation strategies considered in the current study instead of imputation to

10 the mean can improve the prognostic accuracy of downstream models, particularly if multiple imputation is applied. 11 Imputation to the mean should be avoided in future analyses of the INTERMACS registry and analyses where inflexible 12 models are applied.

1. Previous research has also established evidence in favor of applying multiple imputation to improve the prognostic
2. value of risk prediction models. For example, Hassan and Atiya demonstrated superior downstream prediction using
3. an ensemble multiple imputation method on synthetic data with continuous outcomes [64]. Similarly, Nanni et. al
4. demonstrated superior performance in downstream prediction when missing values were imputed using their proposed
5. ensemble multiple imputation method [65]. Notably, the authors artificially induced missing values in these studies and
6. the largest real dataset that was evaluated contained less than 700 observations. An article by Jerez et. al evaluated
7. missing data strategies based on the downstream task of fitting a neural network and predicting early breast cancer
8. relapse [19]. The authors found that KNN imputation led to risk prediction models with the highest discrimination and
9. lowest calibration error. Results from the current study are consistent with these previous findings but also extend their
10. results by providing evidence from a larger source of data (*i.e.,* INTERMACS) and dealing with ‘real-world’ missing 23 values.
11. Others have previously evaluated imputation techniques based on the accuracy with which these techniques impute
12. missing values in the training data [66, 67, 68]. While it is intuitive to hypothesize that more accurate imputation 26 will provide more prognostic downstream models, our results do not support this supposition. For example, when an 27 additional 30% of missing data were amputed, none of the missing data strategies we implemented obtained higher
13. accuracy than imputation to the mean. However, using *any* of the multiple imputation strategies we considered instead
14. of imputation to the mean increased prognostic accuracy of downstream models when an additional 30% of missing data
15. were amputed. This result is likely explained by the bias variance tradeoff. In particular, single imputation techniques 31 may lead to prediction models with lower bias but higher variance than multiple imputation techniques.
16. Strengths and limitations The current analysis has a number of strengths. We leveraged the INTERMACS data
17. registry, comprising one of the largest cohorts of patients who received MCS. We applied a well known resampling
18. method to internally validate modeling algorithms for risk prediction. Last, we made our analysis R code available in a public repository ([https://github.com/bcjaeger/INTERMACS-missing-data)](https://github.com/bcjaeger/INTERMACS-missing-data). Last, the approach presented
19. in this paper provides a general framework that can be applied in other studies where missing data are imputed prior
20. to fitting a risk prediction model. The current analysis should also be interpreted in the context of known limitations.
21. We considered a small subset of existing strategies to impute missing data, and other strategies may have provided
22. stronger improvements compared with imputation to the mean. The models we studied obtained low values of scaled
23. Brier score, indicating low prediction accuracy. It is unclear how results may vary for models with higher prediction
24. accuracy. Also, it was not feasible to use only the training data to impute missing values in the testing data due to a lack
25. of available software. Although the miceRanger package allows imputation of new data using existing models, few
26. software packages for imputation allow users to implement multiple imputation with this protocol. Future analyses
27. should introduce more flexible software and hands-on tutorials so that future investigators can optimize imputation of 11 missing data.
28. Conclusion Selecting an optimal strategy to impute missing values can impact the prognostic accuracy of downstream
29. risk prediction models. In the current analysis, conducting multiple imputation using random forests emerged as an
30. optimal strategy to impute missing values in the INTERMACS data. This investigation can directly inform future
31. analyses of INTERMACS data and provide evidence quantifying the benefit of imputing missing data with sound 16 methodology.

Table 1: Participant characteristics stratified by event status. The majority of patients were male and nearly all mechanical circulatory support devices were left-ventricular assistance devices.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic | Overall | Censored | Cessation of support | Dead | Transplant |
| No. of patients | 14,738 | 6,308 | 310 | 4,204 | 3,916 |
| Age, years | 57 (13) | 57 (13) | 48 (14) | 61 (12) | 53 (12) |
| Sex Female | 21 | 22 | 41 | 22 | 19 |
| Male | 79 | 78 | 59 | 78 | 81 |
| Race White | 66 | 63 | 64 | 71 | 67 |
| Black | 25 | 28 | 27 | 21 | 23 |
| Other | 9.2 | 9.6 | 9.4 | 7.4 | 10 |
| Body mass index | 29 (7) | 29 (7) | 29 (8) | 29 (7) | 28 (6) |
| Device strategy Other | 0.6 | 0.6 | 2.6 | 0.5 | 0.6 |
| Bridge to transplant | 52 | 43 | 51 | 40 | 81 |
| Destination therapy | 47 | 56 | 46 | 60 | 18 |
| LVEDD | 6.83 (1.10) | 6.85 (1.07) | 6.49 (0.93) | 6.69 (1.12) | 6.95 (1.12) |
| Urinary albumin, g/dl | 3.41 (0.64) | 3.42 (0.61) | 3.41 (0.64) | 3.33 (0.66) | 3.49 (0.65) |
| Urinary creatinine, mg/dl | 1.39 (0.68) | 1.36 (0.62) | 1.17 (0.53) | 1.49 (0.77) | 1.35 (0.67) |
| CV pressure | 10.8 (6.2) | 10.4 (6.1) | 9.9 (6.0) | 11.6 (6.5) | 10.7 (6.0) |
| Periphal edema | 35 | 33 | 37 | 44 | 31 |
| BUN, mg/dl | 29 (18) | 28 (17) | 22 (13) | 32 (19) | 28 (18) |
| Bilirubin levels, mg/dl | 1.37 (1.84) | 1.25 (1.14) | 1.28 (1.95) | 1.52 (2.46) | 1.41 (1.97) |
| Device type  Bi-ventricular assistance device | 3.5 | 2.1 | 0.3 | 5.8 | 3.4 |
| Left-ventricular assistance device | 97 | 98 | 100 | 94 | 97 |
| Surgery time, minutes | 292 (113) | 289 (110) | 272 (96) | 320 (128) | 272 (98) |
| CPB time, minutes | 95 (49) | 93 (45) | 88 (38) | 103 (56) | 90 (44) |

*Note:*

Table values are mean (standard deviation) or %

Table 2: Number (percent) of missing values for a selection of predictor variables in the overall population and in subgroups based on event status. Many predictor variables exhibited similar proportions of missing values in different outcome groups, but surgery time was an exception.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Overall | Dead | Transplant | Censored | Cessation of support |
| CV pressure | 7,415 (50.3%) | 2,156 (51.3%) | 2,006 (51.2%) | 3,108 (49.3%) | 145 (46.8%) |
| Surgery time, minutes | 6,125 (41.6%) | 2,246 (53.4%) | 2,007 (51.3%) | 1,713 (27.2%) | 159 (51.3%) |
| Periphal edema | 5,093 (34.6%) | 1,543 (36.7%) | 1,470 (37.5%) | 1,952 (30.9%) | 128 (41.3%) |
| LVEDD | 3,155 (21.4%) | 1,000 (23.8%) | 866 (22.1%) | 1,233 (19.5%) | 56 (18.1%) |
| Urinary albumin, g/dl | 1,014 (6.88%) | 326 (7.75%) | 309 (7.89%) | 359 (5.69%) | 20 (6.45%) |
| CPB time, minutes | 1,010 (6.85%) | 287 (6.83%) | 274 (7.00%) | 421 (6.67%) | 28 (9.03%) |
| Bilirubin levels, mg/dl | 850 (5.77%) | 291 (6.92%) | 237 (6.05%) | 304 (4.82%) | 18 (5.81%) |
| Body mass index | 77 (0.52%) | 26 (0.62%) | 19 (0.49%) | 31 (0.49%) | 1 (0.32%) |
| BUN, mg/dl | 50 (0.34%) | 10 (0.24%) | 8 (0.20%) | 32 (0.51%) | 0 (0.00%) |
| Sex | 24 (0.16%) | 9 (0.21%) | 4 (0.10%) | 11 (0.17%) | 0 (0.00%) |
| Urinary creatinine, mg/dl | 20 (0.14%) | 8 (0.19%) | 4 (0.10%) | 8 (0.13%) | 0 (0.00%) |
| Age, years | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Race | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Device strategy | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Device type | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |

Table 3: Accuracy of strategies to impute artificial missing data. Table values are the median change in accuracy (25th, 75th percentile) relative to the accuracy of imputation to the mean. In general, multiple imputation strategies had lower accuracy than single imputation strategies, and few imputation strategies were more accurate than imputation to the mean.

Nominal variables

Numeric variables

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Single imputation | Multiple imputation | Single imputation | Multiple imputation |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 0 (reference) | — | 0 (reference) | — |
| Hot deck | -0.24 (-0.34, -0.16) | -0.25 (-0.37, -0.18) | -0.35 (-0.53, -0.29) | -0.42 (-0.54, -0.36) |
| K-nearest-neighbors | +0.02 (-0.05, 0.15) | -0.01 (-0.09, 0.11) | +0.01 (-0.01, 0.03) | -0.02 (-0.05, 0.00) |
| Predictive mean matching | -0.15 (-0.34, 0.00) | -0.15 (-0.35, 0.00) | -0.25 (-0.40, -0.20) | -0.26 (-0.35, -0.21) |
| Random forest | -0.15 (-0.26, -0.03) | -0.15 (-0.26, -0.03) | +0.05 (0.03, 0.08) | +0.02 (-0.01, 0.04) |
| Bayesian regression | -0.14 (-0.26, 0.01) | -0.14 (-0.27, 0.01) | -0.30 (-0.41, -0.23) | -0.30 (-0.41, -0.23) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 0 (reference) | — | 0 (reference) | — |
| Hot deck | -0.25 (-0.34, -0.18) | -0.26 (-0.36, -0.18) | -0.34 (-0.46, -0.30) | -0.40 (-0.53, -0.36) |
| K-nearest-neighbors | -0.04 (-0.09, 0.03) | -0.07 (-0.13, 0.00) | -0.02 (-0.03, -0.01) | -0.05 (-0.07, -0.04) |
| Predictive mean matching | -0.18 (-0.38, -0.04) | -0.18 (-0.37, -0.04) | -0.29 (-0.46, -0.24) | -0.29 (-0.40, -0.25) |
| Random forest | -0.18 (-0.28, -0.07) | -0.18 (-0.28, -0.08) | -0.01 (-0.03, 0.01) | -0.03 (-0.06, -0.01) |
| Bayesian regression | -0.17 (-0.29, -0.04) | -0.17 (-0.29, -0.05) | -0.31 (-0.43, -0.27) | -0.31 (-0.43, -0.27) |

Table 4: Median (25th, 75th percentile) change in scaled Brier score when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for mortality. Table values show the scaled Brier score for imputation to the mean. For other imputation strategies, table values show the change in scaled Brier score relative to the scaled Brier score when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. Multiple imputation with random forests leads to the highest scaled Brier score for both models and when 0%, 15%, or 30% of additional data in the training and testing sets were set to missing.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 6.09 (5.71, 6.54) | – | 7.27 (6.83, 7.77) | – |
| Missingness as an attribute | – | – | +0.09 (-0.16, 0.31) | – |
| Hot deck | -0.25 (-0.47, 0.01) | +0.05 (-0.15, 0.24) | -0.24 (-0.46, 0.03) | +0.25 (0.08, 0.45) |
| K-nearest-neighbors | +0.09 (-0.06, 0.23) | +0.18 (0.04, 0.34) | -0.06 (-0.27, 0.18) | +0.28 (0.06, 0.46) |
| Predictive mean matching | -0.30 (-0.53, -0.03) | +0.15 (-0.01, 0.37) | -0.22 (-0.43, 0.14) | +0.34 (0.13, 0.54) |
| Random forest | +0.05 (-0.24, 0.33) | +0.34 (0.12, 0.54) | -0.08 (-0.32, 0.21) | +0.34 (0.14, 0.58) |
| Bayesian regression | -0.35 (-0.61, -0.10) | +0.07 (-0.10, 0.29) | -0.25 (-0.52, 0.05) | +0.29 (0.08, 0.52) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 5.56 (4.95, 6.03) | – | 6.72 (6.13, 7.33) | – |
| Missingness as an attribute | – | – | +0.52 (0.21, 0.77) | – |
| Hot deck | +0.10 (-0.22, 0.46) | +0.49 (0.21, 0.78) | +0.02 (-0.28, 0.33) | +0.58 (0.29, 0.92) |
| K-nearest-neighbors | +0.36 (0.10, 0.65) | +0.53 (0.25, 0.79) | +0.04 (-0.23, 0.36) | +0.42 (0.16, 0.68) |
| Predictive mean matching | +0.03 (-0.32, 0.41) | +0.54 (0.20, 0.90) | +0.21 (-0.25, 0.64) | +0.66 (0.32, 1.12) |
| Random forest | +0.39 (-0.05, 0.75) | +0.76 (0.37, 1.12) | +0.35 (0.01, 0.76) | +0.73 (0.41, 1.06) |
| Bayesian regression | +0.05 (-0.44, 0.44) | +0.49 (0.10, 0.85) | +0.19 (-0.21, 0.59) | +0.58 (0.29, 1.06) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 4.79 (4.11, 5.55) | – | 6.29 (5.67, 7.02) | – |
| Missingness as an attribute | – | – | +0.40 (0.11, 0.75) | – |
| Hot deck | +0.47 (0.03, 0.99) | +0.73 (0.22, 1.38) | +0.10 (-0.24, 0.44) | +0.51 (0.05, 0.99) |
| K-nearest-neighbors | +0.57 (0.23, 0.97) | +0.77 (0.47, 1.18) | -0.09 (-0.44, 0.23) | +0.36 (0.09, 0.67) |
| Predictive mean matching | +0.25 (-0.36, 0.82) | +0.71 (0.16, 1.36) | +0.09 (-0.33, 0.64) | +0.58 (0.06, 1.05) |
| Random forest | +0.62 (0.08, 1.22) | +1.04 (0.39, 1.83) | +0.39 (-0.19, 0.77) | +0.69 (0.27, 1.12) |
| Bayesian regression | +0.22 (-0.40, 0.82) | +0.68 (0.10, 1.28) | +0.10 (-0.44, 0.62) | +0.43 (-0.03, 0.93) |

Table 5: Median (25th, 75th percentile) change in scaled Brier score when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for transplant. Table values show the scaled Brier score for imputation to the mean. For other imputation strategies, table values show the change in scaled Brier score relative to the scaled Brier score when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. While there was very little difference in scaled Brier score values when 0% of additional data were set to missing in the training and testing sets, missingness incorporated as an attribute, predictive mean matching, random forests, and Bayesian regression provided models with higher scaled Brier scores when 15% or 30% of additional missing data were amputed.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 9.35 (8.80, 9.71) | – | 9.00 (8.55, 9.41) | – |
| Missingness as an attribute | – | – | -0.07 (-0.28, 0.13) | – |
| Hot deck | +0.01 (-0.12, 0.15) | +0.06 (-0.04, 0.23) | -0.24 (-0.43, 0.04) | -0.01 (-0.20, 0.17) |
| K-nearest-neighbors | +0.06 (-0.04, 0.17) | +0.08 (0.00, 0.19) | -0.27 (-0.50, -0.05) | -0.05 (-0.20, 0.10) |
| Predictive mean matching | +0.04 (-0.12, 0.19) | +0.14 (0.02, 0.29) | -0.34 (-0.60, -0.10) | -0.06 (-0.23, 0.15) |
| Random forest | +0.03 (-0.10, 0.19) | +0.13 (0.03, 0.29) | -0.32 (-0.50, -0.07) | -0.05 (-0.21, 0.14) |
| Bayesian regression | +0.03 (-0.13, 0.16) | +0.10 (0.00, 0.26) | -0.32 (-0.58, -0.05) | +0.02 (-0.13, 0.25) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 8.76 (8.20, 9.21) | – | 8.01 (7.57, 8.54) | – |
| Missingness as an attribute | – | – | +0.50 (0.27, 0.78) | – |
| Hot deck | +0.25 (-0.04, 0.55) | +0.42 (0.20, 0.78) | -0.10 (-0.34, 0.23) | +0.21 (-0.02, 0.52) |
| K-nearest-neighbors | +0.46 (0.20, 0.73) | +0.54 (0.28, 0.79) | -0.10 (-0.41, 0.20) | +0.12 (-0.12, 0.38) |
| Predictive mean matching | +0.45 (0.10, 0.76) | +0.65 (0.34, 0.94) | -0.03 (-0.34, 0.21) | +0.25 (0.02, 0.62) |
| Random forest | +0.44 (0.12, 0.76) | +0.60 (0.32, 0.95) | -0.07 (-0.35, 0.26) | +0.16 (-0.09, 0.47) |
| Bayesian regression | +0.53 (0.21, 0.79) | +0.74 (0.37, 0.94) | -0.07 (-0.39, 0.24) | +0.24 (-0.09, 0.56) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 7.96 (7.26, 8.63) | – | 7.09 (6.45, 7.68) | – |
| Missingness as an attribute | – | – | +0.83 (0.55, 1.10) | – |
| Hot deck | +0.45 (-0.02, 0.90) | +0.60 (0.15, 1.11) | -0.01 (-0.34, 0.41) | +0.19 (-0.17, 0.65) |
| K-nearest-neighbors | +0.42 (0.00, 0.79) | +0.61 (0.18, 0.90) | -0.21 (-0.54, 0.19) | +0.09 (-0.22, 0.46) |
| Predictive mean matching | +0.70 (0.21, 1.21) | +0.90 (0.46, 1.46) | +0.09 (-0.32, 0.54) | +0.34 (-0.04, 0.85) |
| Random forest | +0.70 (0.14, 1.27) | +0.93 (0.49, 1.45) | -0.13 (-0.46, 0.43) | +0.25 (-0.12, 0.66) |
| Bayesian regression | +0.77 (0.32, 1.40) | +1.00 (0.44, 1.53) | 0.00 (-0.45, 0.52) | +0.24 (-0.17, 0.80) |

Table 6: Median (25th, 75th percentile) change in concordance index when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for mortality. Table values show the concordance index for imputation to the mean. For other imputation strategies, table values show the change in concordance index relative to the concordance index when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. Multiple imputation with random forests led to the highest concordance index for boosting models when 0%, 15%, or 30% of additional data in the training and testing sets were set to missing. For proportional hazards models, multiple imputation with nearest neighbors or random forests was the most effective strategy.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 69.3 (68.9, 69.8) | – | 70.7 (70.3, 71.0) | – |
| Missingness as an attribute | – | – | 0.00 (-0.20, 0.19) | – |
| Hot deck | -0.20 (-0.44, 0.05) | +0.04 (-0.13, 0.27) | -0.19 (-0.36, 0.00) | +0.13 (-0.04, 0.28) |
| K-nearest-neighbors | +0.03 (-0.10, 0.23) | +0.14 (-0.02, 0.36) | -0.10 (-0.30, 0.13) | +0.14 (-0.03, 0.30) |
| Predictive mean matching | -0.34 (-0.56, -0.03) | +0.11 (-0.05, 0.37) | -0.21 (-0.44, 0.05) | +0.21 (0.06, 0.39) |
| Random forest | +0.04 (-0.24, 0.29) | +0.30 (0.08, 0.52) | -0.02 (-0.26, 0.18) | +0.24 (0.07, 0.41) |
| Bayesian regression | -0.39 (-0.69, -0.10) | +0.09 (-0.16, 0.28) | -0.21 (-0.44, -0.02) | +0.22 (0.06, 0.41) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 69.2 (68.8, 69.7) | – | 70.5 (70.1, 71.0) | – |
| Missingness as an attribute | – | – | +0.10 (-0.11, 0.31) | – |
| Hot deck | -0.18 (-0.52, 0.19) | +0.25 (-0.07, 0.58) | -0.23 (-0.50, 0.03) | +0.12 (-0.07, 0.32) |
| K-nearest-neighbors | +0.16 (-0.17, 0.42) | +0.30 (0.05, 0.56) | -0.16 (-0.33, 0.10) | +0.10 (-0.07, 0.31) |
| Predictive mean matching | -0.42 (-0.83, 0.02) | +0.24 (-0.07, 0.53) | -0.26 (-0.54, 0.00) | +0.26 (0.06, 0.43) |
| Random forest | -0.04 (-0.39, 0.26) | +0.41 (0.05, 0.64) | -0.08 (-0.29, 0.19) | +0.27 (0.04, 0.43) |
| Bayesian regression | -0.50 (-0.95, -0.06) | +0.20 (-0.11, 0.47) | -0.29 (-0.48, -0.03) | +0.23 (0.07, 0.43) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 68.9 (68.4, 69.4) | – | 70.2 (69.8, 70.7) | – |
| Missingness as an attribute | – | – | +0.12 (-0.08, 0.31) | – |
| Hot deck | -0.15 (-0.52, 0.30) | +0.12 (-0.23, 0.51) | -0.22 (-0.47, 0.02) | +0.10 (-0.17, 0.32) |
| K-nearest-neighbors | +0.17 (-0.11, 0.49) | +0.33 (0.09, 0.65) | -0.08 (-0.27, 0.16) | +0.19 (-0.01, 0.38) |
| Predictive mean matching | -0.75 (-1.15, -0.34) | +0.06 (-0.29, 0.52) | -0.36 (-0.67, -0.04) | +0.27 (0.04, 0.48) |
| Random forest | -0.29 (-0.80, 0.23) | +0.26 (-0.10, 0.64) | -0.16 (-0.47, 0.11) | +0.29 (0.07, 0.52) |
| Bayesian regression | -0.75 (-1.28, -0.22) | +0.12 (-0.29, 0.48) | -0.36 (-0.70, -0.07) | +0.19 (-0.01, 0.44) |

Table 7: Median (25th, 75th percentile) change in calibration error when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for mortality. Table values show the calibration error for imputation to the mean. For other imputation strategies, table values show the change in calibration error relative to the calibration error when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. As more data in the training and testing sets were set to missing, single and multiple imputation with random forests emerged as the strategies with the lowest calibration error.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 2.41 (1.71, 3.44) | – | 3.29 (2.24, 4.80) | – |
| Missingness as an attribute | – | – | -0.09 (-1.07, 0.65) | – |
| Hot deck | -0.04 (-0.68, 0.58) | -0.45 (-1.25, 0.25) | -0.13 (-1.12, 0.65) | -0.90 (-1.98, 0.01) |
| K-nearest-neighbors | +0.04 (-0.59, 0.65) | -0.29 (-0.80, 0.39) | -0.30 (-1.14, 0.61) | -0.75 (-1.59, 0.14) |
| Predictive mean matching | -0.18 (-0.69, 0.47) | -0.69 (-1.36, -0.03) | -0.11 (-1.27, 0.89) | -1.02 (-2.08, -0.12) |
| Random forest | -0.07 (-0.58, 0.65) | -0.46 (-1.10, 0.17) | -0.56 (-1.38, 0.46) | -1.10 (-2.08, -0.14) |
| Bayesian regression | -0.08 (-0.75, 0.53) | -0.57 (-1.43, 0.02) | -0.26 (-1.08, 0.57) | -0.85 (-1.91, 0.12) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 5.75 (3.74, 8.59) | – | 6.28 (4.17, 9.45) | – |
| Missingness as an attribute | – | – | -2.83 (-4.81, -0.83) | – |
| Hot deck | -2.16 (-4.31, -1.08) | -3.92 (-6.23, -1.72) | -1.66 (-3.82, -0.34) | -3.44 (-5.97, -1.48) |
| K-nearest-neighbors | -2.01 (-3.51, -0.66) | -2.48 (-4.08, -1.14) | -0.61 (-2.28, 0.84) | -2.04 (-3.32, -0.63) |
| Predictive mean matching | -3.83 (-6.40, -1.87) | -3.76 (-6.66, -1.04) | -3.52 (-6.43, -1.67) | -3.50 (-7.09, -1.00) |
| Random forest | -3.80 (-5.75, -2.07) | -4.35 (-6.60, -1.53) | -3.74 (-6.34, -1.34) | -3.92 (-6.29, -1.50) |
| Bayesian regression | -3.76 (-6.45, -1.81) | -3.80 (-6.61, -1.04) | -3.79 (-6.80, -1.39) | -3.27 (-6.40, -0.46) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 9.48 (5.50, 15.3) | – | 7.02 (4.32, 11.3) | – |
| Missingness as an attribute | – | – | -1.61 (-5.29, 0.68) | – |
| Hot deck | -4.95 (-9.18, -2.49) | -6.69 (-12.8, -1.56) | -2.48 (-5.46, -0.31) | -2.48 (-7.18, 0.58) |
| K-nearest-neighbors | -3.47 (-6.42, -1.53) | -4.49 (-7.49, -2.39) | +0.73 (-1.56, 3.27) | -1.47 (-3.59, 0.59) |
| Predictive mean matching | -7.33 (-13.0, -2.61) | -6.09 (-12.3, -0.22) | -2.58 (-7.90, 0.10) | -1.30 (-6.86, 2.29) |
| Random forest | -7.81 (-13.1, -3.63) | -7.39 (-13.4, -2.37) | -3.53 (-7.87, -0.29) | -2.58 (-7.27, 0.44) |
| Bayesian regression | -7.27 (-13.2, -2.44) | -5.91 (-12.8, -0.47) | -3.00 (-7.60, 0.97) | -0.54 (-6.60, 3.08) |

Table 8: Median (25th, 75th percentile) change in concordance index when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for transplant. Table values show the concordance index for imputation to the mean. For other imputation strategies, table values show the change in concordance index relative to the concordance index when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. While there was very little difference in concordance index when 0% of additional data were set to missing in the training and testing sets, missingness incorporated as an attribute, predictive mean matching, random forests, and Bayesian regression provided models with higher concordance indices when 15% or 30% of additional missing data were amputed.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 79.4 (79.0, 79.8) | – | 79.2 (78.9, 79.7) | – |
| Missingness as an attribute | – | – | -0.03 (-0.22, 0.14) | – |
| Hot deck | +0.01 (-0.12, 0.17) | +0.07 (-0.05, 0.23) | -0.24 (-0.40, -0.02) | -0.04 (-0.20, 0.15) |
| K-nearest-neighbors | +0.08 (-0.02, 0.16) | +0.08 (0.01, 0.17) | -0.21 (-0.40, -0.04) | -0.04 (-0.18, 0.10) |
| Predictive mean matching | +0.03 (-0.11, 0.16) | +0.13 (0.01, 0.24) | -0.34 (-0.57, -0.12) | -0.06 (-0.19, 0.16) |
| Random forest | +0.03 (-0.09, 0.17) | +0.15 (0.06, 0.24) | -0.26 (-0.46, -0.08) | -0.02 (-0.16, 0.14) |
| Bayesian regression | +0.01 (-0.15, 0.16) | +0.10 (0.01, 0.22) | -0.32 (-0.54, -0.10) | +0.02 (-0.13, 0.22) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 78.9 (78.5, 79.4) | – | 78.4 (77.9, 78.9) | – |
| Missingness as an attribute | – | – | +0.47 (0.26, 0.71) | – |
| Hot deck | +0.24 (0.04, 0.51) | +0.47 (0.26, 0.76) | -0.13 (-0.40, 0.22) | +0.29 (0.07, 0.58) |
| K-nearest-neighbors | +0.36 (0.21, 0.54) | +0.46 (0.29, 0.62) | -0.13 (-0.39, 0.17) | +0.17 (-0.06, 0.39) |
| Predictive mean matching | +0.32 (0.11, 0.58) | +0.56 (0.37, 0.82) | -0.12 (-0.38, 0.25) | +0.32 (0.14, 0.61) |
| Random forest | +0.32 (0.13, 0.64) | +0.59 (0.36, 0.82) | -0.11 (-0.40, 0.24) | +0.22 (-0.03, 0.51) |
| Bayesian regression | +0.39 (0.17, 0.63) | +0.60 (0.40, 0.83) | -0.15 (-0.46, 0.27) | +0.27 (-0.01, 0.64) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 78.4 (77.7, 78.8) | – | 77.4 (76.8, 78.0) | – |
| Missingness as an attribute | – | – | +0.91 (0.52, 1.24) | – |
| Hot deck | +0.34 (-0.03, 0.72) | +0.74 (0.48, 1.11) | -0.19 (-0.53, 0.34) | +0.55 (0.19, 0.86) |
| K-nearest-neighbors | +0.28 (-0.02, 0.47) | +0.43 (0.21, 0.66) | -0.32 (-0.78, -0.04) | -0.01 (-0.33, 0.31) |
| Predictive mean matching | +0.62 (0.29, 0.98) | +1.02 (0.74, 1.34) | +0.03 (-0.31, 0.44) | +0.65 (0.29, 0.95) |
| Random forest | +0.59 (0.22, 1.00) | +1.04 (0.76, 1.30) | -0.21 (-0.58, 0.15) | +0.36 (0.01, 0.68) |
| Bayesian regression | +0.81 (0.41, 1.08) | +1.10 (0.80, 1.39) | -0.04 (-0.54, 0.37) | +0.47 (0.10, 0.91) |

Table 9: Median (25th, 75th percentile) change in calibration error when different imputation strategies were applied to training and testing sets instead of imputation to the mean prior to developing a risk prediction model for transplant. Table values show the calibration error for imputation to the mean. For other imputation strategies, table values show the change in calibration error relative to the calibration error when imputation to the mean was applied. All table values are multiplied by 100 for ease of interpretability. As more data in the training and testing sets were set to missing, single and multiple imputation with nearest neighbors emerged as the optimal strategy for proportional hazards models while missingness incorporated as an attributed emerged an the optimal strategy for boosting models.

Proportional hazards

Gradient boosted decision trees

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Imputation method | Single Imputation | Multiple Imputation | Single Imputation | Multiple Imputation |
| No additional missing data |  |  |  |  |
| Imputation to the mean | 1.36 (0.92, 2.07) | – | 1.79 (1.34, 2.50) | – |
| Missingness as an attribute | – | – | +0.01 (-0.53, 0.54) | – |
| Hot deck | -0.01 (-0.37, 0.29) | 0.00 (-0.39, 0.26) | +0.11 (-0.56, 0.68) | -0.07 (-0.67, 0.67) |
| K-nearest-neighbors | +0.00 (-0.25, 0.24) | -0.02 (-0.25, 0.21) | +0.09 (-0.40, 0.61) | -0.03 (-0.52, 0.67) |
| Predictive mean matching | -0.04 (-0.34, 0.32) | -0.08 (-0.41, 0.26) | +0.09 (-0.49, 0.63) | -0.04 (-0.63, 0.70) |
| Random forest | -0.06 (-0.39, 0.29) | -0.06 (-0.35, 0.29) | -0.02 (-0.49, 0.63) | +0.02 (-0.54, 0.56) |
| Bayesian regression | -0.01 (-0.40, 0.27) | -0.13 (-0.38, 0.18) | +0.12 (-0.46, 0.78) | +0.24 (-0.46, 1.04) |
| +15% additional missing data |  |  |  |  |
| Imputation to the mean | 2.48 (1.79, 3.93) | – | 2.51 (1.81, 3.29) | – |
| Missingness as an attribute | – | – | -0.50 (-1.38, 0.16) | – |
| Hot deck | -0.76 (-1.95, 0.21) | -0.51 (-2.14, 0.89) | -0.01 (-1.00, 0.66) | +0.69 (-0.47, 1.97) |
| K-nearest-neighbors | -0.82 (-2.01, 0.21) | -0.78 (-1.96, 0.26) | +0.20 (-0.59, 1.01) | +0.23 (-0.73, 1.02) |
| Predictive mean matching | -1.01 (-2.15, 0.27) | -0.46 (-2.16, 0.94) | +0.15 (-0.91, 1.02) | +0.72 (-0.81, 1.87) |
| Random forest | -0.80 (-2.32, 0.51) | -0.59 (-2.03, 0.81) | -0.10 (-1.15, 0.66) | +0.42 (-0.93, 1.34) |
| Bayesian regression | -0.94 (-2.32, 0.58) | -0.64 (-2.04, 0.89) | +0.19 (-0.76, 1.16) | +0.99 (-0.50, 2.27) |
| +30% additional missing data |  |  |  |  |
| Imputation to the mean | 4.98 (3.42, 7.00) | – | 3.99 (2.74, 6.22) | – |
| Missingness as an attribute | – | – | -1.52 (-2.62, -0.35) | – |
| Hot deck | -2.17 (-4.65, 0.10) | -0.49 (-3.74, 2.34) | -0.53 (-2.79, 1.05) | +1.89 (-0.93, 4.76) |
| K-nearest-neighbors | -1.88 (-3.34, -0.22) | -1.88 (-3.70, -0.14) | -0.41 (-1.72, 0.68) | -0.54 (-2.26, 0.88) |
| Predictive mean matching | -1.30 (-4.52, 1.28) | +0.04 (-3.48, 2.70) | -0.05 (-2.54, 2.53) | +1.36 (-1.26, 4.01) |
| Random forest | -1.80 (-4.34, 0.79) | -0.58 (-3.95, 2.18) | -0.55 (-2.64, 1.53) | +0.33 (-2.27, 2.77) |
| Bayesian regression | -1.34 (-4.22, 1.59) | -0.23 (-3.15, 2.61) | -0.16 (-2.47, 1.94) | +0.89 (-1.89, 3.67) |

2618

2383

2158

2040

1929

710

414

0

1000

2000

3000

Intersection Size

CV pressure\_NA

Surgery time\_NA

Peripheral edema\_NA

0

2000

4000

6000

Set Size

Figure 1: An upset plot showing three variables from the INTERMACS registry and all combinations of missing patterns. The bottom left plot shows the number of missing values for each variable, separately. The top right plot shows the number of missing values for each combination of the three variables. For example, there were 2,618 rows in the overall INTERMACS data where both CV pressure and surgery time were missing.

1.000

1.000

1.000

0.999

1.000

0.817

0.985

0.846

0.870

0.772

0.996

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Bayesian

regression

Random

forest

Predictive

mean

matching

K−nearest−

neighbors

Hot deck

Missingness

as an

attribute

0.0

0.5

1.0

Single imputation

Multiple imputation

# Difference in scaled Brier score versus using imputation to the mean

Figure 2: Posterior distribution of differences in scaled Brier score values relative to imputation to the mean when different imputation strategies are applied before fitting a risk prediction model. Results are aggregated over scenarios where the outcome is mortality and transplant and the amount of additional missing data is 0%, 15%, or 30%. Posterior probability that the difference in scaled Brier score exceeds 0, indicating an improvement in overall model accuracy, is printed to the right of each distribution. Each multiple imputation strategy and single imputation with missingness incorporated as an attribute had over 90% posterior predicted probability of increasing the scaled Brier score versus using imputation to the mean.

0.999

1.000

1.000

0.972

0.994

0.063

0.464

0.094

0.511

0.214

0.971

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Pr(Difference >

Bayesian

regression

Random

forest

Predictive

mean

matching

K−nearest−

neighbors

Hot deck

Missingness

as an

attribute

−0.5

0.0

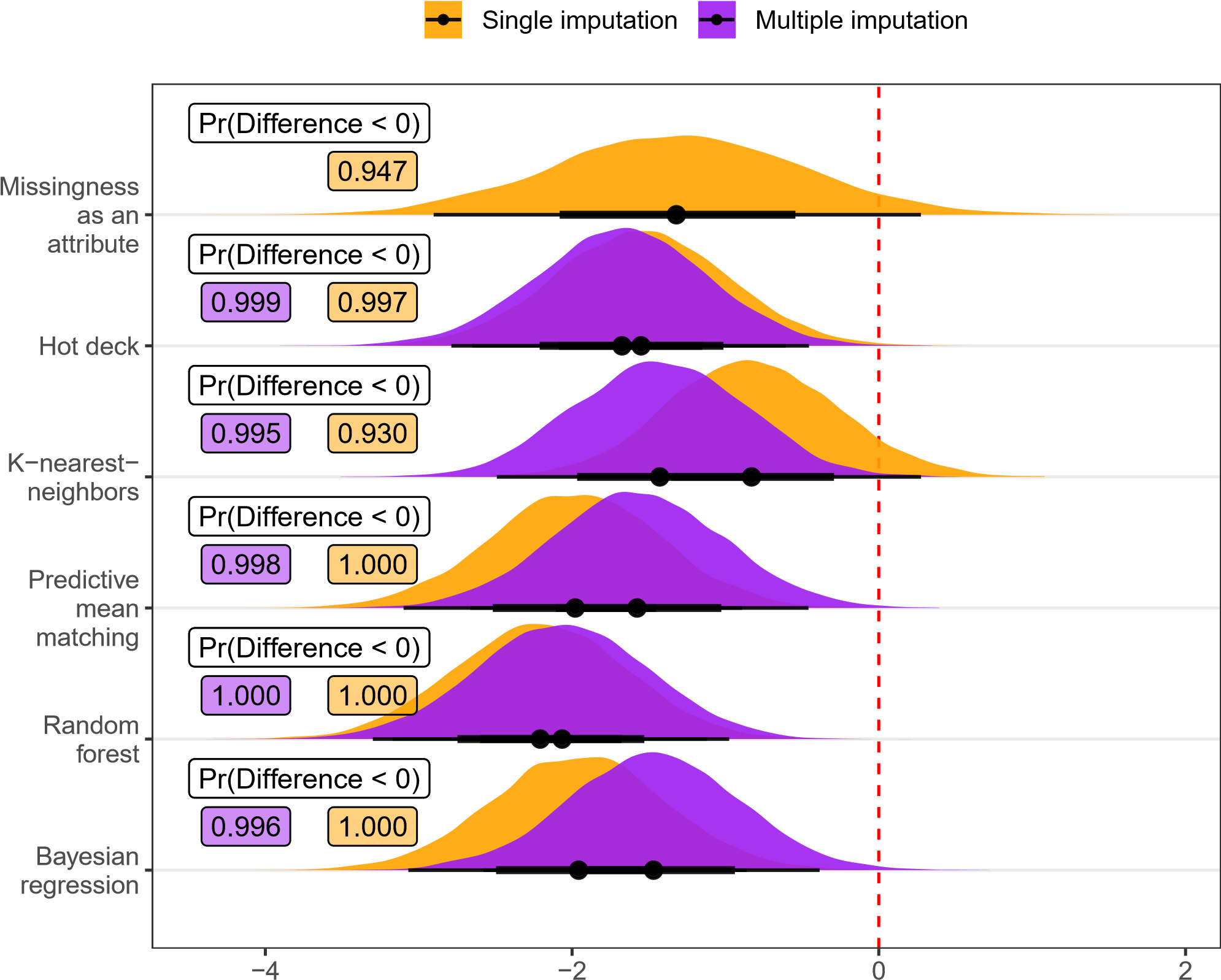
0.5

Single imputation

Multiple imputation

# Difference in concordance index versus using imputation to the mean

Figure 3: Posterior distribution of differences in concordance index values relative to imputation to the mean when different imputation strategies are applied before fitting a risk prediction model. Results are aggregated over scenarios where the outcome is mortality and transplant and the amount of additional missing data is 0%, 15%, or 30%. Posterior probability that the difference in concordance index exceeds 0, indicating an improvement in model discrimination, is printed to the right of each distribution. Multiple imputation with predictive mean matching, random forests, and Bayesian regression each had over 90% posterior predicted probability of increasing the concordance index versus using imputation to the mean.



# Difference in calibration error versus using imputation to the mean

Figure 4: Posterior distribution of differences in calibration error values relative to imputation to the mean when different imputation strategies are applied before fitting a risk prediction model. Results are aggregated over scenarios where the outcome is mortality and transplant and the amount of additional missing data is 0%, 15%, or 30%. Posterior probability that the difference in calibration error is less than 0, indicating an improvement in model calibration, is printed to the right of each distribution. Every imputation strategy evaluated had over 90% posterior predicted probability of improving model calibration versus using imputation to the mean.

## References

1. [1] Emelia J Benjamin, Michael J Blaha, Stephanie E Chiuve, Mary Cushman, Sandeep R Das, Rajat Deo, J Floyd,
2. M Fornage, C Gillespie, CR Isasi, et al. Heart disease and stroke statistics-2017 update: a report from the american 4 heart association. *Circulation*, 135(10):e146–e603, 2017.

5 [2] National Center for Health Statistics. *Health, United States, 2016, With chartbook on long-term trends in health*. 6 Number 2017. Government Printing Office, 2017.

7 [3] Chetan B Patel, Jennifer A Cowger, and Andreas Zuckermann. A contemporary review of mechanical circulatory 8 support. *The Journal of Heart and Lung Transplantation*, 33(7):667–674, 2014.

1. [4] Mark S Slaughter, Joseph G Rogers, Carmelo A Milano, Stuart D Russell, John V Conte, David Feldman,
2. Benjamin Sun, Antone J Tatooles, Reynolds M Delgado III, James W Long, et al. Advanced heart failure treated 11 with continuous-flow left ventricular assist device. *New England Journal of Medicine*, 361(23):2241–2251, 2009. 12 [5] Leslie W Miller. Left ventricular assist devices are underutilized. *Circulation*, 123(14):1552–1558, 2011.

13 [6] Garrick C Stewart and Lynne W Stevenson. Keeping left ventricular assist device acceleration on track. *Circulation*, 14 123(14):1559–1568, 2011.

1. [7] Eileen M Hsich, David C Naftel, Susan L Myers, Eiran Z Gorodeski, Kathleen L Grady, Darlene Schmuhl,
2. Karen L Ulisney, and James B Young. Should women receive left ventricular assist device support? findings from 17 INTERMACS. *Circulation: Heart Failure*, 5(2):234–240, 2012.

18 [8] William G Cotts, Edwin C McGee Jr, Susan L Myers, David C Naftel, James B Young, James K Kirklin, and 19 Kathleen L Grady. Predictors of hospital length of stay after implantation of a left ventricular assist device: An 20 analysis of the INTERMACS registry. *The Journal of Heart and Lung Transplantation*, 33(7):682–688, 2014.

21 [9] Peter Eckman, Andrew Rosenbaum, Haree Vongooru, Jagroop Basraon, Ranjit John, Wayne Levy, et al. Survival 22 of INTERMACS profile 4-6 patients after left ventricular assist device implant is improved compared to seattle 23 heart failure model estimated survival. *Journal of Cardiac Failure*, 17(8):S38–S39, 2011.

1. [10] James K Kirklin, Francis D Pagani, Robert L Kormos, Lynne W Stevenson, Elizabeth D Blume, Susan L Myers,
2. Marissa A Miller, J Timothy Baldwin, James B Young, and David C Naftel. Eighth annual INTERMACS 26 report: Special focus on framing the impact of adverse events. *The Journal of Heart and Lung Transplantation*, 27 36(10):1080–1086, 2017.
3. [11] Robert L Kormos, Jennifer Cowger, Francis D Pagani, Jeffrey J Teuteberg, Daniel J Goldstein, Jeffrey P Jacobs,
4. Robert S Higgins, Lynne W Stevenson, Josef Stehlik, Pavan Atluri, et al. The society of thoracic surgeons
5. INTERMACS database annual report: Evolving indications, outcomes, and scientific partnerships. *The Journal of*
6. *Heart and Lung Transplantation*, 38(2):114–126, 2019.

[12] Luigi Adamo, Yuanyuan Tang, Michael E. Nassif, Eric Novak, Philip G. Jones, Shane LaRue, John A. Spertus, and

Douglas L. Mann. The heartmate risk score identifies patients with similar mortality risk across all INTERMACS

1. profiles in a large multicenter analysis. *JACC: Heart Failure*, 4(12):950–958, 2016.
2. [13] Donald B Rubin. *Multiple imputation for nonresponse in surveys*, volume 81. John Wiley & Sons, 2004.
3. [14] Stef Van Buuren. *Flexible Imputation of Missing Data*. Chapman and Hall/CRC, 2018.
4. [15] Jonathan AC Sterne, Ian R White, John B Carlin, Michael Spratt, Patrick Royston, Michael G Kenward, Angela M 7 Wood, and James R Carpenter. Multiple imputation for missing data in epidemiological and clinical research: 8 potential and pitfalls. *Bmj*, 338, 2009.

9 [16] Joost R van Ginkel, Marielle Linting, Ralph CA Rippe, and Anja van der Voort. Rebutting existing misconceptions 10 about multiple imputation as a method for handling missing data. *Journal of personality assessment*, 102(3):297–

1. 308, 2020.
2. [17] Trevor Hastie, Robert Tibshirani, and Jerome Friedman. *The elements of statistical learning: data mining,* 13 *inference, and prediction*. Springer Science & Business Media, 2009.
3. [18] Max Kuhn and Kjell Johnson. *Feature engineering and selection: A practical approach for predictive models*.
4. CRC Press, 2019.
5. [19] José M Jerez, Ignacio Molina, Pedro J García-Laencina, Emilio Alba, Nuria Ribelles, Miguel Martín, and Leonardo 17 Franco. Missing data imputation using statistical and machine learning methods in a real breast cancer problem. 18 *Artificial intelligence in medicine*, 50(2):105–115, 2010.

19 [20] Julie Josse, Nicolas Prost, Erwan Scornet, and Gaël Varoquaux. On the consistency of supervised learning with 20 missing values. *arXiv preprint arXiv:1902.06931*, 2019.

21 [21] Sunu S Thomas, Nadav Nahumi, Jason Han, Matthew Lippel, Paolo Colombo, Melana Yuzefpolskaya, Hiroo 22 Takayama, Yoshifumi Naka, Nir Uriel, and Ulrich P Jorde. Pre-operative mortality risk assessment in patients 23 with continuous-flow left ventricular assist devices: application of the heartmate ii risk score. *The Journal of* 24 *Heart and Lung Transplantation*, 33(7):675–681, 2014.

25 [22] Melissa J Azur, Elizabeth A Stuart, Constantine Frangakis, and Philip J Leaf. Multiple imputation by chained 26 equations: What is it and how does it work? *International journal of methods in psychiatric research*, 20(1):40–49,

1. 2011.
2. [23] Stef Van Buuren, Jaap PL Brand, Catharina GM Groothuis-Oudshoorn, and Donald B Rubin. Fully conditional 29 specification in multivariate imputation. *Journal of statistical computation and simulation*, 76(12):1049–1064,
3. 2006.
4. [24] Lawrence R Landerman, Kenneth C Land, and Carl F Pieper. An empirical evaluation of the predictive mean
5. matching method for imputing missing values. *Sociological Methods & Research*, 26(1):3–33, 1997.

[25] Jiahua Chen and Jun Shao. Nearest neighbor imputation for survey data. *Journal of Official Statistics*, 16(2):113,

2000.

1. [26] J. C. Gower. A general coefficient of similarity and some of its properties. *Biometrics*, 27(4):857–871, 1971.
2. [27] Rebecca R Andridge and Roderick JA Little. A review of hot deck imputation for survey non-response. *Interna-*
3. *tional statistical review*, 78(1):40–64, 2010.
4. [28] Leo Breiman. Random forests. *Machine Learning*, 45(1):5–32, Oct 2001.
5. [29] Torsten Hothorn, Peter Buehlmann, Sandrine Dudoit, Annette Molinaro, and Mark Van Der Laan. Survival 8 ensembles. *Biostatistics*, 7(3):355–373, 2006.

9 [30] Carolin Strobl, Anne-Laure Boulesteix, Achim Zeileis, and Torsten Hothorn. Bias in random forest variable 10 importance measures: Illustrations, sources and a solution. *BMC Bioinformatics*, 8(25), 2007.

11 [31] Carolin Strobl, Anne-Laure Boulesteix, Thomas Kneib, Thomas Augustin, and Achim Zeileis. Conditional 12 variable importance for random forests. *BMC Bioinformatics*, 9(307), 2008.

13 [32] Hemant Ishwaran, Udaya B Kogalur, Eugene H Blackstone, Michael S Lauer, et al. Random survival forests. *The* 14 *annals of applied statistics*, 2(3):841–860, 2008.

15 [33] Byron C Jaeger, D Leann Long, Dustin M Long, Mario Sims, Jeff M Szychowski, Yuan-I Min, Leslie A 16 Mcclure, George Howard, Noah Simon, et al. Oblique random survival forests. *The Annals of Applied Statistics*, 17 13(3):1847–1883, 2019.

18 [34] Bhekisipho Twala. An empirical comparison of techniques for handling incomplete data using decision trees. 19 *Applied Artificial Intelligence*, 23(5):373–405, 2009.

20 [35] Yufeng Ding and Jeffrey S Simonoff. An investigation of missing data methods for classification trees applied to 21 binary response data. *Journal of Machine Learning Research*, 11(Jan):131–170, 2010.

1. [36] Gareth James, Daniela Witten, Trevor Hastie, and Robert Tibshirani. *An introduction to statistical learning*,
2. volume 112. Springer, 2013.
3. [37] David G Kleinbaum and Mitchel Klein. *Survival analysis*, volume 3. Springer, 2010.
4. [38] Jerome H Friedman. Greedy function approximation: a gradient boosting machine. *Annals of statistics*, pages 26 1189–1232, 2001.
5. [39] Tianqi Chen and Carlos Guestrin. Xgboost: A scalable tree boosting system. In *Proceedings of the 22Nd ACM*
6. *SIGKDD International Conference on Knowledge Discovery and Data Mining*, KDD ’16, pages 785–794, New 29 York, NY, USA, 2016. ACM.

30 [40] Erika Graf, Claudia Schmoor, Willi Sauerbrei, and Martin Schumacher. Assessment and comparison of prognostic 31 classification schemes for survival data. *Statistics in medicine*, 18(17-18):2529–2545, 1999.

1. [41] Kaspar Rufibach. Use of brier score to assess binary predictions. *Journal of clinical epidemiology*, 63(8):938–939,
2. 2010.

[42] Thomas A Gerds and Martin Schumacher. Consistent estimation of the expected brier score in general survival models with right-censored event times. *Biometrical Journal*, 48(6):1029–1040, 2006.

3 [43] Eugene H Blackstone, David C Naftel, and Malcolm E Turner Jr. The decomposition of time-varying hazard into 4 phases, each incorporating a separate stream of concomitant information. *Journal of the American Statistical* 5 *Association*, 81(395):615–624, 1986.

6 [44] Thomas A Gerds, Per K Andersen, and Michael W Kattan. Calibration plots for risk prediction models in the 7 presence of competing risks. *Statistics in medicine*, 33(18):3191–3203, 2014.

8 [45] Thomas A Gerds, Michael W Kattan, Martin Schumacher, and Changhong Yu. Estimating a time-dependent 9 concordance index for survival prediction models with covariate dependent censoring. *Statistics in Medicine*, 10 32(13):2173–2184, 2013.

1. [46] Max Kuhn and Kjell Johnson. *Applied predictive modeling*, volume 26. Springer, 2013.
2. [47] Alessio Benavoli, Giorgio Corani, Janez Demšar, and Marco Zaffalon. Time for a change: a tutorial for comparing 13 multiple classifiers through bayesian analysis. *The Journal of Machine Learning Research*, 18(1):2653–2688,
3. 2017.
4. [48] Alexander Lex, Nils Gehlenborg, Hendrik Strobelt, Romain Vuillemot, and Hanspeter Pfister. Upset: visualization 16 of intersecting sets. *IEEE transactions on visualization and computer graphics*, 20(12):1983–1992, 2014.

17 [49] Guido Van Rossum and Fred L Drake Jr. *Python reference manual*. Centrum voor Wiskunde en Informatica 18 Amsterdam, 1995.

1. [50] SAS Institute Inc. 2013. *SAS® 9.4 Statements: Reference*. Cary, NC: SAS Institute Inc.
2. [51] William Michael Landau. The drake r package: a pipeline toolkit for reproducibility and high-performance 21 computing. *Journal of Open Source Software*, 3(21), 2018.

22 [52] Nicholas Tierney, Di Cook, Miles McBain, and Colin Fay. *naniar: Data Structures, Summaries, and Visualisations* 23 *for Missing Data*, 2020. R package version 0.6.0.

24 [53] Stef van Buuren and Karin Groothuis-Oudshoorn. mice: Multivariate imputation by chained equations in r. 25 *Journal of Statistical Software*, 45(3):1–67, 2011.

26 [54] Sam Wilson. *miceRanger: Multiple Imputation by Chained Equations with Random Forests*, 2020. R package 27 version 1.3.5.

1. [55] Byron C. Jaeger. *table.glue: Make and Apply Customized Rounding Specifications for Tables*. R package version
2. 0.0.2.
3. [56] Hadley Wickham, Mara Averick, Jennifer Bryan, Winston Chang, Lucy D’Agostino McGowan, Romain François,
4. Garrett Grolemund, Alex Hayes, Lionel Henry, Jim Hester, Max Kuhn, Thomas Lin Pedersen, Evan Miller,
5. Stephan Milton Bache, Kirill Müller, Jeroen Ooms, David Robinson, Dana Paige Seidel, Vitalie Spinu, Kohske Takahashi, Davis Vaughan, Claus Wilke, Kara Woo, and Hiroaki Yutani. Welcome to the tidyverse. *Journal of Open Source Software*, 4(43):1686, 2019.
6. [57] Ben Goodrich, Jonah Gabry, Imad Ali, and Sam Brilleman. rstanarm: Bayesian applied regression modeling via
7. Stan., 2020. R package version 2.21.1.
8. [58] Matthew Kay. *tidybayes: Tidy Data and Geoms for Bayesian Models*, 2020. R package version 2.1.1.
9. [59] Terry M Therneau. *A Package for Survival Analysis in R*, 2020. R package version 3.2-7.
10. [60] Max Kuhn and Hadley Wickham. *Tidymodels: a collection of packages for modeling and machine learning using* 8 *tidyverse principles.*, 2020.

9 [61] Thomas Alexander Gerds and Brice Ozenne. *riskRegression: Risk Regression Models and Prediction Scores for* 10 *Survival Analysis with Competing Risks*, 2020. R package version 2020.02.05.

11 [62] Byron C. Jaeger. INTERMACS-missing-data. Available at https://github.com/bcjaeger/intermacs-missing-data. 12 DOI: 10.5281/zenodo.4247449, 2020.

1. [63] Cheaha - UABgrid documentation. Available at https://docs.uabgrid.uab.edu/wiki/cheaha. Last accessed: 2020-11-
2. 03.
3. [64] Mostafa M Hassan, Amir F Atiya, Neamat El-Gayar, and Raafat El-Fouly. Regression in the presence missing 16 data using ensemble methods. In *Neural Networks, 2007. IJCNN 2007*, pages 1261–1265. IEEE, 2007.

17 [65] Loris Nanni, Alessandra Lumini, and Sheryl Brahnam. A classifier ensemble approach for the missing feature 18 problem. *Artificial intelligence in medicine*, 55(1):37–50, 2012.

19 [66] Gerhard Tutz and Shahla Ramzan. Improved methods for the imputation of missing data by nearest neighbor 20 methods. *Computational Statistics & Data Analysis*, 90:84–99, 2015.

21 [67] Todd D Little, Terrence D Jorgensen, Kyle M Lang, and E Whitney G Moore. On the joys of missing data. *Journal* 22 *of pediatric psychology*, 39(2):151–162, 2013.

1. [68] Andrew J Steele, Spiros C Denaxas, Anoop D Shah, Harry Hemingway, and Nicholas M Luscombe. Machine
2. learning models in electronic health records can outperform conventional survival models for predicting patient
3. mortality in coronary artery disease. *PloS one*, 13(8):e0202344, 2018.