Discovery of Biomarkers for Coronary Microvascular Disease

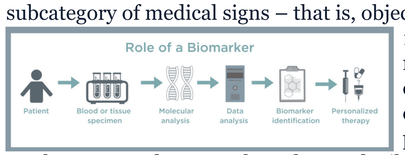
Saumya Agrawal, Alicia Arredondo Eve, Justina Zurauskiene, and Zeynep Madak-Erdogan

Student Pushing Innovation Program, National Center for Supercomputing Applications, University of Illinois at Urbana-Champaign

INTRODUCTION

Coronary microvascular disease (CMD) is heart disease that affects the walls and inner lining of tiny coronary artery blood vessels that branch off from the larger coronary arteries. This research is vital because although CMD is vastly common in women, the only method of identification we have is the elimination of the other possibilities such as coronary artery disease.

Biomarkers The term "biomarker, refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient which can be measured accurately and reproducibly.



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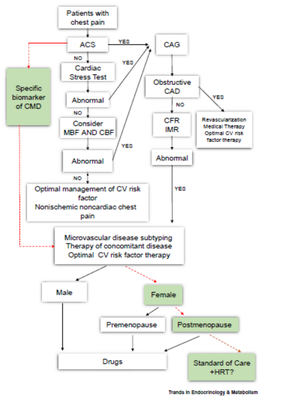


Figure 3. Modified Chest Pain Evaluation Diagram.
Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; CBF, cerebral blood flow; CFR, coronary flow reserve; CMD, coronary microvascular disease; IMR, index of microcirculatory resistance; MBF, myocardial blood flow.

This research is vital because currently, the identification of CMD is subject to the elimination of the other similar possibilities such as Coronary Artery Disease (CAD).

With definite biomarkers for CMD, we could eliminate the need for a stress test, or a coronary angiography by optimizing testing and treatment.

DATA OVERVIEW

The raw data consisted of 71 patients and 594 features. These features were in the form of targeted and untargeted metabolites, and general health data.

1. Coronary Microvascular Disease (CMD)
2. Coronary Artery Disease (CAD)
3. Control Group

The patients were divided into 3 groups. The value of the 'Group' feature determined the condition of the patient.

METHOD

Pre-processing Pipeline

The data needs to be cleaned prior to the analysis. We did this programmatically in Python, so that the code can be re-used for future similar datasets.

Creating reduced models by removing features with more than 20% and 40% missing data

Removal of any feature which had more than 20% or 40% missing values.

Feature Scaling using Min-Max Normalization

For clustering, all values needed to be scaled to a defined range

Gaussian Mixture clustering to find ideal K value for K nearest neighbor imputation

Clustering allowed us to use the K value of 3

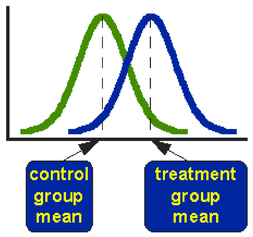
Performing KNN imputation and creating two datasets with 20% and 40% imputed values.

We ended up with two datasets to perform analysis on.

Biomarker Discovery

In Python, a dictionary of three data frames was created with each data frame only containing data from one of the groups.

After that, a difference in means T test was performed for each of the features between the groups.

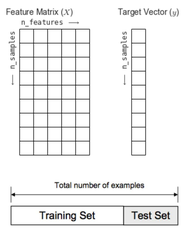


Whichever features had a significant difference (p value < 0.05) between the groups, were considered potential biomarkers.

65 potential biomarkers were discovered in this manner

Machine Learning

Machine learning algorithms were used to validate the efficacy of the discovered biomarkers.



These datasets were divided into their respective feature matrices (containing all potential biomarkers) and their target arrays (group numbers).

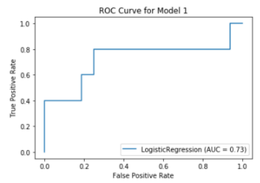
30% of the total datasets were used for testing and the remaining 70% for training the model.

Three models were created: Logistic Regression training model, Decision Tree training model, and Random Forest training model. Based on their respective efficacies, the Logistic Regression Model was picked for this study.

Logistic Regression Model: Specifications

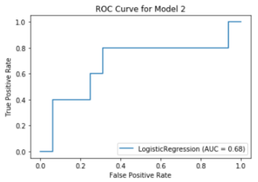
- Penalty = 'l1'. L1 or Lasso regularization was performed which reduces overfitting
- C = 0.8, Inverse regularization strength
- Class Weight = balanced.
- Solver = 'liblinear' is an algorithm which applies automatic parameter selection

Receiver Operator Curve (ROC) and AUC score



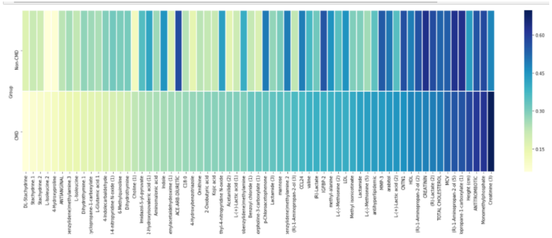
A receiver operator curve shows the trade off between sensitivity (or true positive rate) and specificity (1-false positive rate).

Area under curve is a common approach to judge the ROC curve. In general, an **AUC** of 0.5 suggests no discrimination, 0.7 to 0.8 is considered acceptable



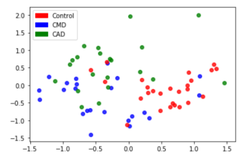
We can see from the above plotted curves, only the dataset with only 20% of the data imputed has an acceptable AUC score, so henceforth only that dataset is used.

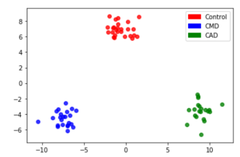
Graphical Verifications



The heatmap above shows the mean values of each biomarker for the CMD and Non CMD groups. We can see that some biomarkers have a very significant difference

On the right side, we have the Principal Component Analysis performed on all the biomarkers





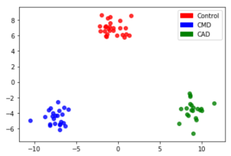
On the left side, we have the Linear Discriminant Analysis performed on all the biomarkers

RESULT

This analysis discovered 65 biomarkers for Coronary Microvascular disease.

The ROC and AUC graphs help us choose the dataset with imputation performed only on the dataset with features with at most 20% missing data.

The Logistic Regression Model had a training accuracy of 87.76% and a testing accuracy of 86.72%. This indicated that overfitting was overcome in the machine learning Model.



The Linear Discriminant Analysis shows a very clear distinction between all three groups: patients with CMD, patients with CAD, and control group patients.

These results along with the Heatmap and Principal component analysis verifies the efficacy of the discovered biomarkers.

CONCLUSIONS

One sided tests also need to be performed to identify what biomarkers lean to what level for each group. For example, does a higher or lower level of Lactamide indicate the presence of Coronary Microvascular disease? We can also use the same methodology for the discovery of biomarkers for other diseases.

ACKNOWLEDGEMENTS

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