

Dear Editor and reviewers,

Thank you for your kind letter and for the reviewer's comments concerning our manuscript "Prediction of permanent pacemaker implantation after transcatheter aortic valve replacement; the role of Machine Learning" (Manuscript No: 81836). Greatly appreciate all the valuable comments and your help in improving the paper.

Please find the descriptions below on revision based on the comments from the reviewers:

Reviewer's comments:

Reviewer 1:

1. Kindly mention full forms before writing the short - forms, like TTE, RF etc. 2. Add details of your ML - Algorithm used and how its decision tree structure works? 3. Add a Table comparing the sensitivity and specificity of your AI Model vs other Models. 4. Improve grammar and language. 5. What this study adds to already available literature is not mentioned? 6. Names of all variables is missing from your manuscript. 7. How the Images or variables were graded and or annotated and by whom?

Comment 1:

1. Kindly mention full forms before writing the short - forms, like TTE, RF etc.

Response: Thank you so much for your comments. We have revised all the full forms like TTE to "Transthoracic Echocardiogram", GBM to "gradient boosting algorithm" according to your comments.

Comment 2:

Add details of your ML - Algorithm used and how its decision tree structure works?

Response: Thank you for your comments. Details of the algorithm have been now mentioned in the manuscript as per your suggestions as follows:

"The *caret* R package was used to fit a GBM model from the *gbm*³ R package using 5-fold cross-validation repeated 10 times. Model hyperparameters, specified prior to fitting the model, are tunable variables that control the chosen model's learning process. The hyperparameters tuned were the interaction depth, number of trees, and shrinkage. The minimum number of observations required at each node was fixed at 20. Figures 2 and 4 include the top 20 variables that indicate which have the highest predictive power in classifying those with events and those without events."

Comment 3:

Add a Table comparing the sensitivity and specificity of your AI Model vs other Models.

Response: Thank you for your comments. We have added sensitivities and specificities now as per your suggestions.

Comment 4:

Improve grammar and language

Response: Thank you for your comments. We have revised the manuscript in terms of grammar and punctuation throughout.

Comment 5:

What this study adds to already available literature is not mentioned?

Response: Thank you for your comments. We revised the manuscript as per your suggestions and added the following: "Brachiocephalic artery to aortic valve annulus distance to height ratio was the highest

weighted predictor for PPM implantation post-TAVR at both one month and one year. As far as we are aware, we are the first to describe this variable as a predictor for PPM requirements”.

Comment 6:

Names of all variables is missing from your manuscript.

Response: Thank you for your comments. We have mentioned all the variables missing in the manuscript in the supplementary index.

Comment 7:

How the Images or variables were graded and or annotated and by whom?

Response: Thank you for your comments. We have now added “Marlene Girardo and Matthew Buras are the statisticians who ran the analysis who are also authors of the paper” according to your comments.

#Reviewer 2:

In this study, authors were used supervised ML with the random forest machine learning model to predict pre-procedural risk for PPM post-TAVR at 30 days and 1 year. If the authors complete minor revisions, the quality of the study will be further improved. 1. pg 6: "The model was optimized using 5 fold cross-validation repeated 10 times." - I don't understand why you repeated 5-fold cross-validation 10 times. If you describe this sentence more specifically, it will help readers understand. 2. Authors should describe the fine tuning used in the random forest model in more detail.

Comment 1:

pg 6: "The model was optimized using 5-fold cross-validation repeated 10 times." - I don't understand why you repeated 5-fold cross-validation 10 times. If you describe this sentence more specifically, it will help readers understand.

Answer: Thank you for your comments. We revised our manuscript according to the suggestion and improved the abstract as follows: “The model was optimized using 5-fold cross-validation repeated 10 times to get the highest prediction accuracy”.

Comment 2:

Authors should describe the fine-tuning used in the random forest model in more detail.

Answer: Thank you for your comments. We have revised our manuscript as per your suggestions and we have elaborated the methods section and the models have been described in more detail now as follows: “.Model hyperparameters, specified prior to fitting the model, are tunable variables that control the chosen model’s learning process. The hyperparameters tuned were the interaction depth, number of trees, and shrinkage. The minimum number of observations required at each node was fixed at 20. Figures 2 and 4 include the top 20 variables that indicate which have the highest predictive power in classifying those with events and those without events. The study population for PPM risk was limited to those that had a trans-femoral or trans-apical approach. The PPM risk score developed by Vejpongsa *et al*^[20] uses 6 factors. Each factor had points associated that collapsed into a three-group score (low, moderate, or high risk). Tuning of hyperparameters optimizes the target metric, that metric being the area under the receiver operating characteristic curve (AUC)”.

Thank you so much reviewers and the editors once again for your valuable comments and help in improvement of the script.

Sincerely,
Sai Harika Pujari,
Internal Medicine Resident,
The Brooklyn Hospital Center, NY.

