Peer Review File

Article Information: Available at http://dx.doi.org/10.21037/jmai-20-50

Review Comments

The manuscript entitled *Developing a Machine Learning Algorithm Using Isolated STS Database Variables to Predict the Presence of Clinically-Significant Ischemic Mitral Regurgitation* examined the association of *STS Database* variables with the presence of clinically significant ischemic mitral regurgitation in patients undergoing coronary artery bypass grafting. The results show that STS Database variables have a predictive association with the presence of clinically significant IMR in patients, which may have potential as predictive variables in future translational machine learning modeling to assist in directing surgical care. This study has certain clinical application guidance value. However, there are still some minor issues that need to be addressed before the paper is accepted for publication.

Comment 1: The surgical reports of these 416 patients were reviewed. The study cohort was limited to patients with ischemic causes of mitral regurgitation. How can retrospective studies reduce or avoid the effects of bias?

Reply 1: This is an excellent comment. As the reviewer appropriately points out, all retrospective studies suffer from the effects of bias. It was precisely because of this concern that we noted this potential for bias in our "limitations" section. That being said, such retrospective studies serve a vital purpose in building the foundation for more targeted prospective randomized clinical trials. It is precisely upon the foundation of retrospective studies that hypotheses for critical prospective trials originate and are subsequently engineered, implemented, and analyzed. We have tried to minimize the impact of potential bias by the isolated investigation of only patients with a documented ischemic origin to their mitral regurgitation. Patients with complex *structural* disease who require complex reparative techniques are therefore excluded. Since only a simple mitral repair technique is required in ischemic mitral regurgitation (either valve replacement of annuloplasty repair), the bias against performing the very complex repairs by inexperienced surgeons is eliminated (such as those required in Barlow's Syndrome, for instance). Additionally, so-called "loss to follow-up" bias is minimized in our investigation by our mandated, protocolized, and validated (quality-checked) prospective acquisition of all clinical data, including all follow-up data. In fact, although this investigation is indeed a retrospective analysis, the very nature of the STS Database—in which *prospectively* acquired data is meticulously acquired in real time for every patient involved in the study—certainly mitigates many of the points of potential bias (such as "misclassification" and "recall" biases) common to retrospective trials. Further, since participation in the STS Database is mandated, "differential-referral" and "self-selection" biases are also mitigated. Further, the elimination of author bias, by exclusion of any authors with potential bias toward the outcome of the study is also essential in randomized trials. We appreciate the reviewer's appropriate concern and hope that we have achieved as unbiased an investigation as possible. We have made changes in the *Limitations* section of the manuscript regarding the minimalization of bias.

Changes in the text: Added to *Limitations* section of manuscript: *"Even though this is a retrospective analysis, the very nature of the prospective acquisition of mandatory, rigidly structured STS Database variables mitigates many potential biases, including recall, misclassification, self-selection, and differential referral biases."*

Comment 2: The unique ability of machine learning algorithms to detect previously unrecognized and counterintuitive associations between patient specific clinical variables and clinically significant disease processes (such as IMR) makes it a promising approach for clinical research. What are the requirements of machine learning algorithms for computer hardware and software?

Reply 2: The machine learning models developed in this study utilized standard machine learning and deep learning algorithms that, like essentially all machine learning algorithms, are available for free download from their various internet sites. The deep learning analysis, for instance, was implemented using Keras, which is readily available from its Google supported website. None of our machine learning models require advanced and expensive graphics processing units (GPU's) or tensor processing units (TPU's). All patient-specific ischemic mitral regurgitation models can be implemented on simple CPU's, such as those found in a standard MacIntosh or PC laptop.

Changes in the text: The methods section was modified with the addition of the following text: *"All analyses were carried out on laptop computers using only standard CPU's."*

Comment 3: Surgical treatment of ischemic mitral regurgitation (IMR) is still a challenging clinical problem with many unresolved clinical disputes. What are the new advances in the treatment of IMR?

Reply 3: This is an especially pertinent comment, since this clinical area is changing rapidly. Ischemic mitral regurgitation continues to be an important clinical problem, complicating at least a third of patients with acute myocardial infarction. Although most resolve their severe ischemic mitral regurgitation, those that do not require intervention to prolong expected life without symptoms. Clinical trials have demonstrated that even a moderate amount of residual longstanding mitral regurgitation is deleterious in regard to asymptomatic survival. Although recent data suggest that regional contractile information may be predictive regarding which patients will have a durable response to standard mitral annuloplasty repair, the potentially additive predictive power of STS Database variables in machine learning models to direct surgical decision-making is strongly supported by our investigation. The recent FDA clinical approval of the application of catheter-based MitraClip technology resulted in its immediate clinical application in ischemic mitral regurgitation patients. Since this catheter-based repair is actually based upon a type of *surgical* mitral repair and is still therefore subject to many of the patient-specific factors that impact mitral repair (such as the influences of residual ischemic myocardial substrate and regional left ventricular remodeling) it is highly likely that the clinical direction of this catheter-based application will also be assisted by the predictive potential of the STS Database variables that are associated with the recurrence of ischemic mitral regurgitation.

Changes in the text: The discussion section of the manuscript was modified by the addition of the following text: *"Even as minimally invasive catheter-based mitral valvular repair*

strategies are clinically adopted, post-repair recurrence secondary to progressive regional LV remodeling will continue to make these STS Database machine learning models clinically relevant in the management of these patients."

Comment 4: Develop a machine learning algorithm that uses isolated STS database variables to predict the presence of clinically significant ischemic mitral regurgitation. What is the prospect of clinical transformation of this technology?

Reply 4: The infrastructure necessary to implement this technology on a widescale basis is already in place. Essentially every cardiac surgical program in the United States and many throughout the world have been longstanding participants in the STS Database with years of experience in handling their institutional data acquisition. (STS Database participation is mandated by the majority of third-party healthcare payers in the US.) Further, the machine learning models necessary for individual patient surgical decision-making can be downloaded onto almost any MacIntosh or PC computer. All of the analyses performed for our data analysis were performed on standard laptop CPU's.

Changes in the text: We appreciate the reviewer's implication of the importance of the clinical application of this predictive potential and have stressed the direct clinical application of this methodology in several prominent places in the manuscript. Further, at the reviewer's recommendation, we have added the following clarifying text as the final summary statement of the manuscript: *"The capability of STS Database variables to characterize the clinical, mechanical, phenotypic, and myocardial substrates associated with the occurrence of ischemic MR places it in a prominent position to contribute to the immediate development and clinical implementation of models to predict the patient-specific risk of persistence or post-repair recurrence of ischemic MR."*

Comment 5: Machine learning can be used to solve the choice of cardiac surgical intervention types to maximize the durability of IMR, which is still a challenge for cardiac surgeons. What is the clinical effect of this method?

Reply 5: A clinical tool into which cardiovascular clinicians can enter patient-specific STS Database variables to calculate patient-specific likelihood of long-term durability of mitral annuloplasty repair would allow mitral repair (ideal option when compared to valve replacement) in all patients in whom repair will be durable, thereby limiting the use of valve *replacement* to only those patients who absolutely need it for long-term mitigation of their mitral insufficiency. As mentioned, it is our strong belief that high-density left ventricular regional contractile indices are also predictive of repair durability and will be combined with this STS Database prognostic machine learning model. Further, standard *Electronic Health Record* (EHR) data may also be additive to these predictive machine learning modeling capabilities.

Changes in the text: We appreciate the reviewer's suggestion that we further clarify the implementation and potential impact of the machine learning models enabled by this investigation. The following text has been added to the introductory section of the manuscript: *"The robust, all-inclusive capabilities of current machine learning models allow the combination of variables from multiple clinical sources, thereby maximizing the strength of the models by including a wide diversity of variable content and source."*

Comment 6: Although many advantages of mitral valve repair make it the most common choice, 38.60% of patients with mitral valve repair received IMR experience and relapsed or died after 2 years of follow-up. The reliable predictors of valve repair failure still have important clinical significance. How to avoid the failure of repair? How to improve the prediction efficiency of machine learning algorithms?

Reply 6: As also discussed above, the reviewer is exactly correct in identifying the future of the inclusion of patient-specific clinical variables from multiple sources with widely varying formats into machine learning models that will very literally include the majority (if not all) of the clinical factors that impact the presence or recurrence of ischemic mitral regurgitation. Our model alone markedly improves this clinical accuracy in predicting the metabolic, phenotypic, and clinical substrate associated with ischemic mitral regurgitation. Its combination with other clinically available variables to more accurately direct surgical intervention is expected to push the accuracy of predicting which patients will have a durable result from mitral repair into the 90-95% range. This degree of accuracy would profoundly change the clinical paradigm in the surgical management of all patients with ischemic mitral regurgitation.

Changes in the text: As noted above, we have added the following text to the manuscript regarding this very helpful comment by the reviewer: *"The capability of STS Database variables to characterize the clinical, mechanical, phenotypic, and myocardial substrates associated with the occurrence of ischemic MR places it in a prominent position to contribute to the immediate development and clinical implementation of models to predict the patient-specific risk of persistence or post-repair recurrence of ischemic MR."*

Final comment to the reviewers:

Once again, we would like to thank the reviewers for their informed, thoughtful, and helpful comments. We believe that the manuscript has been significantly improved by our collaboration with the reviewers and hope that they will find it suitable for publication in the Journal of Medical Artificial Intelligence.