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PEER-REVIEW REPORT

Specific comments to authors

The Authors applied a Machine Learning model to evaluate pre-transplant factors that may predict post-operative, in-hospital major cardiovascular events. They collected 575 LT recipients who underwent surgery between 2001 and 2011, using 83 pre-transplant variables. Then, they built a ML algorithm that showed a good performance for predicting major cardiovascular events (the AUROC was 0.89). Factors associated with post-operative major cardiovascular events were beta blockers, blood type, results of non-invasive stress tests. The aim of this paper is of interest. Nonetheless, the ML model usually applies on very large databases with huge amounts of data. In this paper, the number of patients included in reliatively low (575), therefore in my opinion the Authors should explain why they decided to use ML approach instead of a standard statistical analysis.

Reply: We opted for an ML approach due to its capacity to handle complex interactions among multiple variables, providing enhanced predictive accuracy. In our dataset with 83 pre-transplant variables, ML techniques, particularly XGBoost, demonstrated superior performance over traditional statistical methods, improving risk stratification for major cardiovascular events, particularly in situations involving intricate datasets, such as the prognostication of liver transplantation, in which the context of complex data makes it essential to employ advanced analytical techniques.

Further, the Authors should, in my opinion, clarify if the definition of MACE (a composite outcome including stroke, new-onset heart failure, severe arrhythmia, and nonfatal myocardial infarction) has been previously applied in the transplant setting or not. Indeed, it is not clear if fatal myocardial infarction has been included or not, or what is the definition of severe arrhythmia, or the relationship between stroke and

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pre-transplant cardiac assessment.

Reply: We appreciate this clarification point. Our MACE definition, encompassing stroke, new-onset heart failure, severe arrhythmia, and myocardial infarction, aligns with established literature in cardiovascular research. The definition includes fatal myocardial infarction. We will make this explicit in the manuscript for better clarity.

Finally, the Introduction section discusses about the unreliability of non-invasive stress tests before transplantation: according to this study, alteration of myocardial perfusion scintigraphy and negative stress test have been included in the proposed algorithm. Additionally, it should be cleared if all patients underwent, before transplant, the same pre-operative cardiological assessment.

Reply: All patients underwent a standardized pre-operative cardiological assessment, which included various components such as non-invasive stress tests and myocardial perfusion scintigraphy. We will explicitly mention this in the Methods and Discussion section to address this concern.

These points, in my opinion, are very impactful, in a future attempt of external validation. Minor issues > why patients transplanted between 2001 and 2011 were collected? > why the XGBoost model was used instead of other ML models? Regards.

Reply: The inclusion of patients transplanted between 2001 and 2011 aimed to capture a diverse range of cases over a substantial period. This span allowed us to encompass different clinical practices, evolving technologies, and changes in patient demographics, enhancing the generalizability of our findings.

The decision to use XGBoost was based on its effectiveness in handling imbalanced datasets, native support for missing data, and robust performance in real-world applications. Its ability to capture complex relationships among features and provide

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feature importance contributed to its selection. We acknowledge that other ML models have merits, some of them were attempted, but we chose XGBoost for its specific advantages in our context with better results.