Reply to Unlocking the future: machine learning sheds light on prognostication for early-stage hepatocellular carcinoma

Running Head: Reply to Unlocking the future

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Conflict of interest statement
Dear editor,

We extend our sincere appreciation to Dai and colleagues for their insightful commentary on our article.¹ We are also grateful for the opportunity to engage with their valuable insights and perspectives.

Personalized prognostication, particularly utilizing non-invasive biomarkers, has emerged as a focus in recent studies across various liver diseases, including hepatocellular carcinoma (HCC), viral hepatitis and metabolic dysfunction-associated fatty liver disease (MAFLD). For example, Lu et al. developed an algorithm employing eXtreme Gradient Boosting (XGBoost) to predict treatment failure of direct-acting antivirals among patients with chronic hepatitis C.² Verma et al. utilized machine learning techniques with clinical and anthropometric data to differentiate the risk of severe fibrosis in NAFLD patients, demonstrating superior performance compared to traditional markers such as fibrosis 4 (FIB-4) in Asian cohorts.³ Kim et al. also developed a machine learning based risk score to predict HCC occurrence in patients with chronic hepatitis B.⁴ These advancements in personalized prognostication provide clinical physicians with additional tools beyond conventional guidelines and staging systems to assess patients and predict their prognoses.

Machine learning has emerged as a convenient and effective method for developing prognostic models, demonstrating remarkable performance in several
previous studies. Scholars and clinical physicians have promoted its application in clinical settings, encompassing diagnosis, pre-treatment evaluation, post-treatment monitoring, and prognostication. For example, the liver stiffness measure (LSM)-plus model combines LSM with a machine learning algorithm to accurately diagnose metabolic dysfunction-associated steatotic liver disease (MASLD)-related cirrhosis and advanced fibrosis. Additionally, Kwong et al. developed a model using random forest model and Spearman's correlation analyses to predict waitlist dropout among patients with HCC. He et al. developed a model integrating random forest, support vector machine, classical decision tree and conditional inference tree to predict the adverse outcome of patient after liver transplantation. These applications of machine learning underscore its potential to enhance various stages of clinical management, promising significant advancements in patient care.

In addition to the Least Absolute Shrinkage and Selection Operator (LASSO) regression method performed in our study, other methods such as decision tree and random survival forest have been utilized for survival analysis and model development. We echo with Dai et al.'s suggestion regarding the evaluation of alternative machine-learning methods and emphasize the importance of assessing the clinical applicability in developing models. Depending on the modeling approach and outcome event settings, the predictive performances might be diverse among
the different models. For example, risk scores showed excellent ability on stratification of patients into risk groups among different diseases and decision tree and random survival forest excel in predicting outcome events.\textsuperscript{11,12} When utilized effectively, machine learning holds the potential to revolutionize clinical practice and propel us further into the era of precision medicine.

In the development of our risk score, we integrated both conventional Cox proportional hazard model and machine learning based LASSO Cox regression. While Cox logistic regression has traditionally been a robust tool in survival analysis, its accuracy may be compromised by variable interactions.\textsuperscript{13} LASSO Cox regression had shown ability on addressing the problem of multicollinearity among variables, thus emerging as a common approach for evaluating survival factors. Our study confirms the efficacy of LASSO regression and paves the way for further research in risk stratification and patient management.

Over the years, numerous non-invasive serum biomarker scores have been developed to provide clinical insight into patients’ disease status. These scores often combine serum biochemical data, such as the albumin bilirubin (ALBI) score, FIB-4 score, and model for end stage liver disease (MELD) score, each serving specific clinical purposes and having distinct limitations. For instance, the FIB-4 score evaluates the status of fibrosis in patients with chronic hepatitis,\textsuperscript{14} while the MELD
score assesses severity and prognosis in patients with end-stage liver diseases. In our analysis, we incorporated these index variables to indicate clinical status and weight their significance. We concur with Dai et al.'s suggestion to explore and compare the performance of risk scores when incorporating these indices as a whole or integrating individual components within each index. This analysis will enable us to elucidate the interactions among different factors influencing the prognosis of HCC patients.

In conclusion, we once again express our gratitude to Dai et al. for their insightful commentary and perspective. We are committed to further refining machine-learning based models for diagnosing and predicting the outcomes of liver diseases, leveraging non-invasive biomarker and image features. With the collaborative efforts of analysts and machine learning, we anticipate significant advances in personalized medicine of diseases and devote ourselves to “unlock the future”.
Reference


