Letter to the Editor

Necessity of integrating statistical inference and clinical practice in developing clinical models: bias introduced by neoadjuvant chemotherapy

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We read the article by Dr. Lam *et al.* (1). This article is a multicenter study involving Cox multivariable models with the least absolute shrinkage and selection operator (LASSO) to construct a survival prediction model for colorectal liver metastasis (CRLM) patients after hepatectomy. A total of 572 patients were enrolled, and two full models for overall survival (OS) and recurrence-free survival (RFS) consisting of the same eight novel variables were developed. This study provides a strong prediction for the survival of CRLM patients after hepatectomy, offering valuable guidance for clinical decision-making. However, after carefully reading this article, we have the following comments.

First, the author mentions that in their findings, due to the heterogeneity involved in the use of neoadjuvant chemotherapy, patients with a worse disease status tend to receive more neoadjuvant chemotherapy, ultimately resulting in an association between preoperative neoadjuvant chemotherapy and poorer OS and RFS. We fully agree with this phenomenon, which has also been reported in previous studies (2,3). However, the author should not include neoadjuvant chemotherapy as a negative variable affecting OS and RFS in their models. Specifically, a worse disease status leads to poorer OS and RFS, and this subset of patients is more likely to receive neoadjuvant chemotherapy, which ultimately manifests as poorer OS and RFS in patients undergoing neoadjuvant chemotherapy. Therefore, the actual reason for the deterioration of OS and RFS is not the neoadjuvant chemotherapy itself but the fact that these patients in the dataset have a worse disease status, which leads to poorer OS and RFS. From a statistical perspective, this is a result of selection bias when using neoadjuvant chemotherapy. When neoadjuvant chemotherapy was applied to CRLM patients without selection bias and was included in the Cox regression model for analysis, the results were more convincing.

Second, we note that the differentiation was based on the new Edmondson grading. However, to the best of our knowledge, the Edmondson grading for differentiation was used for primary carcinoma of the liver (4). Since CRLM and primary carcinoma of the liver have completely different pathologic types, does applying Edmondson grading to CRLM cause bias?

Third, the development of all clinical models was intended for application in clinical practice. However, we are uncertain about how to use these two models in a clinical setting. Why does not the author consider providing formulas or an online calculator to assist with the application of this model?

Finally, I would like to thank Dr. Lam *et al.* for their study on the survival prediction of CRLM patients after hepatectomy, which presented a promising machine learning algorithm to individualize prognostications for patients following resection of CRLM with good discriminative ability. We believe that these machine learning methods will

play an important role in postoperative outcome prediction in patients with malignant tumors.

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Footnote

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