Application of nomogram containing log odds of metastatic lymph node in gallbladder cancer patients

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We thank Choi *et al.* for their great editorial commentary on our recently published article "*A New Nomogram in Predicting the Prognosis of Gallbladder cancer patients after Surgery from SEER database*" (1).

Aimed to the question "*It would be more reasonable to analyze except the patients with stage M1 because they have not achieved curative surgery*". We make the following explanation. The purpose of our article is to evaluate the prognostic value of LODDS system and traditional N staging and to establish a prognosis nomogram on this basis for gallbladder cancer patients after surgery. The selection criteria for samples in our study were patients with lymph node resection information, including curative and noncurative surgery. Many studies suggested that even for advanced gallbladder cancer patients without distant metastases, aggressive surgery is the best way to improve the prognosis, and lymph node dissection is routinely recommended for surgical patients (2-4). According to NCCN guideline, lymph node dissection is necessary for

resectable gallbladder cancer patients. First, it can make the N stage more accurate and help us to judge the prognosis for patients. Second, standard lymphatic dissection may improve the prognosis of patients. And for patients with distant metastasis, as described by professor Choi, curative surgery and lymph node resection are usually not recommended (5,6). Because of this treatment method for M1 stage patients, T and N stage information of M1 stage patients is often incomplete, so it is always difficult to conduct TNM staging for M1 stage patients, and it is also difficult to predict the prognosis for them through TNM staging. However, we found that many M1 stage patients also underwent surgery and lymph node dissection during analyzing the data we downloaded from SEER database. These patients were most likely to have had distant metastases at preoperative or intraoperative, but have not been diagnosed until after "curative surgery (including lymph node dissection)". We think this group of patients has great value, which can provide detailed TNM staging

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information of M1 stage patients and make up for the shortage of postoperative studies on M1 stage patients. In addition, we established another nomogram after removing M1 patients according to professor Choi's suggestion. We found that the C index of the nomogram in the training set was 0.735, and the AUC values of the ROC predicted 1, 3 and 5 years' OS were 0.775, 0.799 and 0.784, respectively, compared with the previous nomogram including M stage, the C index (0.752) and the AUC values of the ROC predicted 1, 3 and 5 years' OS were 0.804, 0.820 and 0.804, respectively. After removing M1 patients, the accuracy of the nomogram is decreased. So, we think that the M1 patients of this study should be retained.

We agree with professor Choi's suggestion that some prognostic factors should be added to this study. However, due to the limited clinical information contained in the SEER database, it is difficult for us to add more prognostic factors to complement the nomogram. For example, the SEER database lacks open information on chemotherapy regimens and does not contain data on tumor markers of patients in this study, such as CA-199, etc. In addition, most of the clinical factors that may impact on prognosis have been collated and statistically analyzed. And the nomogram with six independent prognostic factors (age, tumor size, grade, T stage, M stage and LODDS system) in this study had a good accuracy. Besides, many other studies on prognosis of various cancer including gallbladder cancer have also selected similar clinical factor to us (7-10). Converse, if we include too many clinical factors, due to the lack of the complete information, we have to remove many samples, which would make the sample size smaller and lead to a decline of the nomogram accuracy. As a clinical tool to predict prognosis, nomogram needs to be convenient and practical. Incorporating too many clinical factors will make nomogram complicated, which is not conducive to its application in clinical practice.

Finally, in view of professor Choi's opinion that we did not consider the number of LNs excised during LN staging, we reply as follows. The log odds of metastatic lymph node (LODDS) is defined as log [(the number of positive lymph nodes (PLNs) +0.05)/(the number of negative nodes +0.05)]. LODDS has been studied in a variety of tumors (11,12), precisely because it takes into account both the number of PLNs and resected lymph nodes (RLNs) and compared with lymph node ratio (LNR), it can provide more accurate prediction when all the lymph nodes examined were positive. This article aimed to study the predictive capacity of LODDS and establish a prognosis nomogram for gallbladder cancer patients who received lymph node dissection.

Limited by the sample size and clinical information in the SEER database, there are still some deficiencies in our research. We need to collect more samples and clinical information to make the nomogram more reliable. But through the analysis of the existing data, we believe that as an independent prognostic factor for gallbladder cancer, LODDS has a better prognostic effect than the other three N stages, and the nomogram including LODDS also has certain clinical significance.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-2020-91). DH serves as an unpaid editorial board member of *Annals of Translational Medicine* from Oct 2018 to Sep 2020. QX serves as an unpaid Section Editor of *Annals of Translational Medicine* from Oct 2019 to Sep 2020. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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