



Editorial on “A new nomogram from the SEER database for predicting the prognosis of gallbladder cancer patients after surgery”

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Gallbladder cancer (GBC) is the most common cancer of the biliary tract and has a poor prognosis (1). To date, the treatment that can be expected to cure GBC is surgical resection, and lymph node (LN) metastasis is one of the most important factors for predicting prognosis after surgical resection (2). The most widely used method for evaluating the LN stage is N stage of the American Joint Committee on Cancer (AJCC) cancer staging system. In the AJCC 7th edition, LN staging of GBC was determined to N1 or N2, depending on the location of the metastasized LN (3). However, several studies on GBC have shown that LN staging based on the number of metastasized LNs is more favorable for prognostic prediction than LN staging based on the location of the metastasized LNs (4-6). Reflecting these findings, LN staging of GBC in AJCC 8th edition was classified as N1 (metastases to one to three regional LNs) or N2 (metastases to four or more regional LNs) according to the number of metastasized LN, not the location of metastasized LN (7). This LN staging method, based on the number of metastasized LNs, has the disadvantage that the LN stage can be underestimated if the number of LNs resected during surgery is not sufficient. In this regard, the AJCC 8th edition recommends resection of at least six LNs for GBC surgery (8).

There is another method of assessing the LN status,

called LN ratio (LNR), which is defined as the ratio of the number of metastasized LNs to the total number of LNs resected. The LNR differs from the AJCC 8th edition in that it considers the total number of resected LNs as well as the number of metastasized LNs. The weakness of the LNR is that if there are no metastasized LNs, the value of the LNR is 0, regardless of the total number of LNs that have been resected. In addition, no matter how many metastasized LNs are, if the number is equal to the number of resected LNs, the value of LNR is 1. One way to overcome these shortcomings of LNR is the LN scoring system called log odds of positive lymph nodes (LODDS). LODDS is the log value of the ratio of the metastasized LN and the non-metastasized LN, calculated as: $\log [(the\ number\ of\ metastasized\ LNs + 0.05)/(the\ number\ of\ non-metastasized\ LNs + 0.05)]$. This LODDS scoring system was first introduced in gastric and colorectal cancer and showed better at predicting prognosis than the LNR or AJCC scoring system (9-11).

Xiao *et al.* compared the accuracy of predicting survival of the four LN staging systems mentioned above after surgical treatment of GBC. In this study, the authors identified that LODDS is the best indicator of the LN stage, and based on this, created a nomogram that predicts the prognosis after surgical treatment of GBC. The authors

retrospectively analyzed the data of 1,321 patients with GBC who underwent surgical resection for the period from 2010 to 2014 based on the Surveillance, Epidemiology, and End Results (SEER) database; Patients were randomly assigned 925 to the training set and 396 to the validation set. LN stages were analyzed using AJCC's 7th and 8th editions, LNR and LODDS. In univariate Cox analysis, all these four scoring systems correlated with overall survival. LODDS showed the best accuracy in prognostic prediction when comparing these four LN scoring methods using Akaike Information Criterion (AIC), C-Index, and receiver operating characteristic (ROC) curve analysis. And multivariate Cox analysis, including only LODDS among the LN scoring methods, showed that age, T stage, M stage, LODDS, tumor size, and grade were independent prognostic factors. The authors created an overall survival prediction nomogram using these six factors that were significant in multivariate analysis, and suggested that this new nomogram, including the LODDS system, is a great model for predicting the prognosis of surgically treated GBC patients. In addition, the authors verified this again with a validation set.

The authors should be praised for suggesting a new prognostic nomogram including the LODDS system that showed the best accuracy of LN staging of GBC. However, there are some points to consider about this study. First, the study subjects need to be reviewed. The baseline characteristics of the subjects in this study showed that the M1 stage was 13.5%, which is a significant portion of the total study patients. In fact, patients with stage M1 are those who have not achieved curative surgery. Therefore, if the aim of this study was to evaluate the prognostic value of various N staging systems and develop a prognostic model after curative surgery, it would be more reasonable to analyze except the patients with stage M1.

Second, it is necessary to analyze some additional factors that may affect the prognosis of surgically treated GBC patients. R0 resection and adjuvant chemotherapy or chemoradiotherapy are known to be closely associated with the prognosis of patients with GBC who have undergone surgical treatment (12-15). However, there is no information on R0 resection or adjuvant treatment in this study, and it is not clear whether the same results will be obtained even when all these factors are considered.

Third, this study did not consider the number of LNs excised during LN staging. Since the LN stage is greatly influenced by the number of LNs excised, it is important to consider the number of LNs excised when establishing

LN staging. For example, in N staging of the AJCC 8th edition, when the number of resected LNs is 3 or less, the N2 stage can never be reached, so the LN stage may be underestimated. Regarding LODDS, you can think that LODDS will not be affected by the number of resected LNs as it is the logarithm of the ratio of metastasized and non-metastasized LNs. However, a recent study by Lee *et al.* suggests that the LODDS system is suitable for predicting the prognosis of GBC patients when there are six or more resected LNs (16). In addition, in a study of 1,124 GBC patients using the SEER database, Amini *et al.* reported that the LODDS system outperformed other LN scoring systems when four or more LNs were examined (17). Considering these results, it can be inferred that the number of resected LNs is important even when using LODDS system. Therefore, it is necessary to examine whether there are differences in prognostic predictions depending on the number of resected LNs in this study.

Moreover, the criteria for stratification of LNR or LODDS in several studies, including this study, are not clear and vary from study to study. These obscure criteria for LODDS stratification make prognostic analysis difficult with LODDS systems in real practice. Further clear stratification of LODDS through large-scale studies is necessary for the actual clinical application of LODDS systems.

Despite these concerns, it is meaningful that the authors presented an important new prognostic model in surgically treated GBC patients. And since all the factors included in the prognostic nomogram presented in this study are commonly available in clinical practice, this new prognostic nomogram can be helpful in real clinical practice by overcoming the aforementioned concerns through further investigation.

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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.2020.03.182>). The 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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