

Dear editors and reviewers,

Thank you for the opportunity to revise our manuscript entitled “Establishment and validation of nomograms to predict the risk of ovarian metastasis in gastric cancer: based on a large cohort” (NO: 57212). We greatly appreciate the editor’s and reviewer’s valuable and constructive comments. We agree with these comments and have listed point-by-point responses to the editors and reviewers, and have revised the manuscript accordingly, which we believe has greatly improved the quality of the manuscript.

We would like to re-submit this revised manuscript to *World Journal of Clinical Cases*, and hope that it is acceptable for publication. Please contact us if there is any further revision required. Thank you for your further consideration and we look forward to hearing from you at your earliest convenience.

Yours Sincerely,

Lin Chen, MD, PhD

Point-to-point authors' reply to the reviewers' requests

Reviewer #1

1. Language mistakes were noted and the manuscript should be revised by native speaker

Response: Thank you for your opinion, we have corrected the language mistakes appropriately and revised the manuscript by native speaker.

2. the study design is not clear with repetition of previous work and no new data obtained.

Response: Thank you for your opinion, the purpose of our study design is to construct an evaluable model for early detection of ovarian metastasis in gastric cancer, and the nomogram model has never been reported so far to our knowledge. Although the analysis of clinicopathological features of gastric cancer with ovarian metastasis has been reported previously in a few clinical studies, the number of cases included in the relevant studies is generally small and the analysis of clinical characteristics is not comprehensive. In our study, we selected 18 clinical factors related to ovarian metastasis of gastric cancer for analysis based on previous reports and clinical practice, especially included some immunohistochemical values and serum indicators such as ER, PR, CA125, NLR, etc. None of these new data had been reported for in-depth analysis to our knowledge. In addition, the most important innovation and highlight of our study is the establishment of a recurrence risk prediction model, which could predict the risk of ovarian metastasis in female patients with gastric cancer. The nomogram model is of great guiding value in clinical practice, and the clinical implementation of this model is simple and significant.

3. ambiguous results without no clear explanation how the results between univariate and multivariate analysis were obtained.

Response: Thank you for the careful review. We may not describe the result in full detail in the text, while the results of univariate and multivariate analysis were showed

in Table.1 and Table.2. Our results showed the independent risk factors for ovarian metastasis which were obtained through statistical analysis of a large cohort, and a prediction nomogram model for ovarian metastasis in gastric cancer patients was constructed.

Details on each of these results are explained as follows. Eighteen related clinical factors of 1696 cases were collected and analyzed, and the outcome variables are ovarian metastasis and non-ovarian metastasis. The results of univariate analysis were obtained by using different statistical methods according to the data types of different clinical variables, and the univariate analysis showed that age, Lauren type, whether primary lesion containing signet-ring cell, vascular tumor emboli, T stage, N stage, immunohistochemical ER expression, immunohistochemical PR expression, serum CA125 and NLR were the risk factors for ovarian metastasis of gastric cancer (all $P < 0.05$). The multivariate COX proportional regression model was applied to variables with differences by univariate analysis, we concluded that age ≤ 50 years, Lauren typing of non-intestinal, gastric cancer lesions containing Signet-ring cell components, N stage $> N2$, positive immunohistochemical ER expression, serum CA125 > 35 U/mL, and NLR > 2.16 were independent risk factors (all $P < 0.05$). Independent risk factors were constructed into a nomogram model by R language software. Consistency index (C-index) after continuous correction is 0.840 [95%CI (0.774-0.906)]. After the internal self-sampling (Bootstrap) test, the calibration curve of the model was obtained with an average absolute error of 0.007. The receiver operating characteristic curve (ROC) of the obtained model was drawn. The area under the curve (AUC) was 0.867, The maximal Youden index was 0.613, the corresponding sensitivity was 0.794, and the specificity was 0.819. The highlight of the results section is the process of model construction and validation, the model has been proved to have great predictive efficacy and good clinical applicability.

4. The results are limited and not informative.

Response: The purpose of this study was to analyze clinicopathological features and establish a risk prediction model through statistical analysis. Research ideas were clear

and definite. The results were concise and detailed which could support the research conclusions. The data, instead of being verbose, are illustrative. In the next step, we will carry out multi-center studies and include more cases for analysis, so as to verify the scientific rationality of the prediction model prospectively. We believe the results will be much richer at that time.

Reviewer #2

1. The authors have excluded those who had distant metastasis other than ovary and peritoneum metastasis. Thus, the prevalence of ovarian metastasis in overall population may have been higher than that reported in their study. Please describe the numbers of included and excluded patients. If available, the prevalence of ovarian metastasis in excluded patients should be also described (if not available, not necessary). The exclusion criteria should be briefly explained in the abstract.

Response: Thank you for the careful review and insightful suggestion. We entirely agree with these opinions. In our study, gastric cancer patients who had distant metastasis other than ovary and peritoneum metastasis were not involved, which might have a negative effect on predictive efficacy of the nomogram model due to the worse stage and more complex metastasis mechanism. The whole cohort was a continuous collection of data. According to the exclusion criteria, 546 patients (including 27 patients with ovarian metastasis of gastric cancer) were excluded in the data collection stage of this study, and the 27 patients with ovarian metastasis of gastric cancer also had metastasis of other organs (liver, lung, brain, etc.). The exclusion criteria had been explained in the abstract. Thank you again.

2. In the abstract, they mentioned “treatment options are controversial” and “the high-risk population should pay attention to the possibility of ovarian metastasis during reexamination, to detect and treat as early as possible”. In my opinion, when radically treated patients develop ovarian metastasis as the only site of recurrence, the diagnosis of ovarian metastasis is quite important. On the other hand, when ovarian metastasis is found in patients with advanced gastric cancer who are

receiving palliative chemotherapy or best supportive care alone, the significance of ovarian metastasis is unclear. Please describe more clearly the importance of making diagnosis of ovarian metastasis and how it influences the treatment strategy for gastric cancer.

Response: Thank you for your thoughtful comments. Firstly, ovarian metastasis was a special distant metastasis in gastric cancer, and the mechanism was not clear so far. In clinical practice, we had found that some patients with early stage of gastric cancer can develop ovarian metastasis, while some patients with advanced gastric cancer do not have ovarian metastasis, which showed that tumor stage does not play a decisive role in the occurrence of ovarian metastasis. The main purpose of our study was to establish a predictive model for ovarian metastasis in gastric cancer patients. Secondly, the early detection of ovarian metastasis might provide more treatment options (metastasectomy, cytoreductive surgery, HIPEC, etc.). Some studies had shown that appropriate cytoreductive surgery(CRS) combined with HIPEC could prolong survival time to some extent in the patients with advanced gastric cancer. Early diagnosis is also important for patients with advanced gastric cancer with ovarian metastasis, and the MDT can provide a better plan for these patients to achieve optimal survival time.

Reviewer #3

The authors reported a retrospective study of female patients with gastric cancer to analyze risk factors of ovarian metastasis. Eventually, some factors including high age, more than 6 lymph node metastasis, non-intestinal type, signet-ring cell carcinoma, etc. were found to be associated with ovarian metastasis. The nomogram model of the risk evaluation was constructed. Since this manuscript is well written and shows very clear conclusions, it should be accepted immediately.

Response: Thank you for your careful review and high evaluation, your comments are a great encouragement to us.