Dear editors and reviewers:

Thank you very much for a thorough and careful review of our manuscript entitled: "Development and validation of a nomogram for predicting metachronous peritoneal metastasis in colorectal cancer: a retrospective study" (no:80325). Your kind suggestions substantially improve the quality and readability of our manuscript. We have made revision according to your comments.

Response to editors: Thank you very much for providing us a chance to revise this manuscript. We have finished the revision of the manuscript and repolished it in the professional English language editing companies that you recommend. We have uploaded all of the required accompanying documents *via* the F6Publishing system. Thank you again for your support and advice.

Reviewer #1: The article is aimed to establish and validate a nomogram model for predicting the occurrence of metachronous peritoneal metastasis in colorectal cancer within 3 years after surgery. The title is "Development and validation of a nomogram for predicting metachronous peritoneal metastasis in colorectal cancer: a retrospective study". 1. This is a retrospective study. 2. Several factors influence the outcome of the study. Please discuss these. 3. Please review the literature and add more details in the discussion section. 4. Please also add more details of this nomogram model. 5. What is the new knowledge of the study? 6. Please recommend to the readers "How to apply this knowledge?".

Response to reviewer #1: Thank you very much for your commons. Your valuable suggestions greatly improve the scientific rigor and quality of our manuscript.

1. This is a retrospective study.

   Reply: Thank you for this observation. In this study, the training and

validation cohorts were obtained retrospectively from the Second Hospital of Jilin University. Therefore, the nomogram requires further validation in multi-centered and prospective clinical studies. We acknowledge that this is a limitation of our present study.

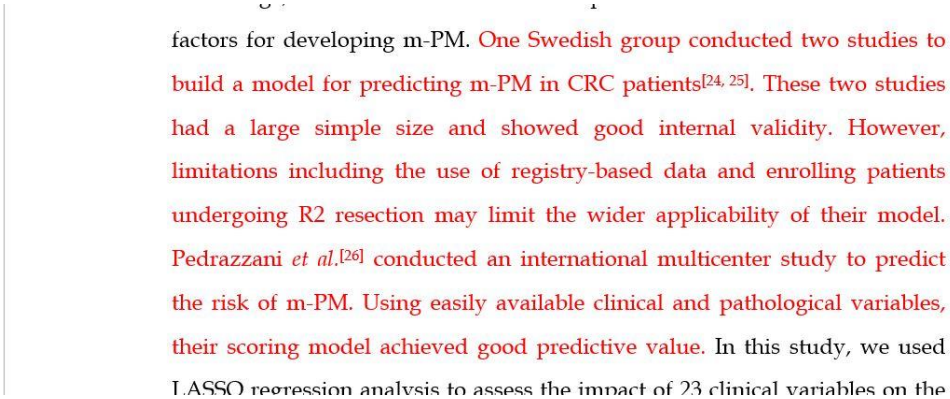
2. Several factors influence the outcome of the study. Please discuss these.

Reply: Thank you for this reminder. We think that there are three main factors that may affect the outcome of this study. First, the present study was a single-centered, retrospective, and non-randomized study. This may limit the global applicability of the model, although this model achieved a good prediction accuracy on both the training and validation cohorts. Second, the diagnosis of m-PM was mainly based on post-operative imaging examinations such as CT. This could lead to a delayed diagnosis because of the limited sensitivity of CT in detecting small peritoneal nodules. But we think this limitation is minor because the main purpose of this study is to identify risk factors affecting m-PM within the follow-up period, and establish a predictive model for early detection in future clinical practice. Third, the follow-up time in this study is relatively limited. Further research is recommended to investigate the risk factors for m-PM at different times points after primary surgery. We have added this part in discussion section, which is marked in red.

This study had some limitations. First, the training and validation cohorts were obtained retrospectively from a single center. Therefore, the nomogram requires further validation in multicenter prospective clinical studies. Second, the diagnosis of m-PM was mainly based on postoperative imaging such as CT. This could have delayed diagnosis because of the limited sensitivity of CT in detecting small peritoneal nodules. However, we believe this limitation was minor because the main purpose of this study was to identify risk factors affecting m-PM within the follow-up period, and establish a predictive model for early detection in future clinical practice. Third, because of the limited follow-up time of the included patients in this study, we could only assess the risk of developing m-PM within 3 years after surgery. Although the typical chronological span of m-PM occurrence was covered, further research is still recommended to investigate the risk factors for m-PM at different times points after primary surgery. ↵

3. Please review the literature and add more details in the discussion section.

   Reply: Thank you for this suggestion. We have reviewed the previous literature on the same topic and mentioned them in the discussion section. Among them, one Swedish group conducted two studies to build a model for predicting m-PM in CRC patients (PMID: 24410859 and 26588669). These two studies had a large simple size and showed good internal validity. However, limitations including the use of registry-based data and enrolling patients undergoing R2 resection may limit the wide applicability of their model. Pedrazzani *et al.* (PMID: 35789302) conducted an international multicenter study to predict the risk of m-PM. Using easily available clinical and pathological variables, their scoring model achieved good predictive value. The revision is marked in red. We think this revision make our study more detailed and objective. Thank you again for your kind suggestion.



factors for developing m-PM. One Swedish group conducted two studies to build a model for predicting m-PM in CRC patients[24, 25]. These two studies had a large simple size and showed good internal validity. However, limitations including the use of registry-based data and enrolling patients undergoing R2 resection may limit the wider applicability of their model. Pedrazzani *et al.*[26] conducted an international multicenter study to predict the risk of m-PM. Using easily available clinical and pathological variables, their scoring model achieved good predictive value. In this study, we used LASSO regression analysis to assess the impact of 23 clinical variables on the

4. Please also add more details of this nomogram model.

   Reply: Thank you for this suggestion. We have provided the specific score for each variable. The scores for the tumor site were rectal cancer = 0, left colon cancer = 32, and right colon cancer = 72. For the histological subtype, the scores were adenocarcinoma = 0, mucinous adenocarcinoma = 57, and signet-ring = 97. For pathological T stage, the scores were T1 = 0, T2 = 31, T3 = 43, and T4 = 100. For CA125, the scores were normal level = 0 and elevated level = 40. For BRAF mutation, the scores were wild type = 0 and mutation = 49. For MSI status, the scores were MSI-L/MSS = 0 and MSI-H = 49. We evaluated the scores of all patients and used the ROC curve and

Youden index to identified the cutoff value of this model. This cutoff value was 168. Then, all patients were divided into two subgroups: low-risk group (risk score ≤ 168) and high-risk group (risk score > 168) (Table 3). Most of the patients (712 cases, 81.1%) were classified in low-risk group. The percentage of patients developing m-PM in this subgroup was 5.6%. Using this simple grouping mothed, our nomogram model can achieve a high negative predictive rate (94.4%). The revision is marked in red.

multivariate regression analysis is illustrated in Figure 3. The scores for the tumor site were rectal cancer = 0, left colon cancer = 32, and right colon cancer = 72. For the histological subtype, the scores were adenocarcinoma = 0, mucinous adenocarcinoma = 57, and signet-ring = 97. For pathological T stage, the scores were T1 = 0, T2 = 31, T3 = 43, and T4 = 100. For CA125, the scores were normal level = 0 and elevated level = 40. For BRAF mutation, the scores were wild type = 0 and mutation = 49. For MSI status, the scores were MSI-L/MSS = 0 and MSI-H = 49. We evaluated the scores of all patients and used the ROC curve and Youden index to identified the optimum cutoff value of this model. This cutoff value was 168. All patients were divided into two subgroups: low-risk group (total score ≤ 168) and high-risk group (total score > 168) (Table 3). Most of the patients (712 cases, 81.1%) were classified into the low-risk group. The percentage of patients developing m-PM in this subgroup was 5.6%. Using this simple grouping mothed, our nomogram model can achieve a high negative predictive rate (94.4%). The calibration curve showed

Table 3 Subgroup analysis of the risk of m-PM

	m-PM		*P* value
	no	yes	
Low-risk group	672 (94.4%)	40 (5.6%)	<0.001
High-risk group	112 (67.5%)	54 (32.5%)	

5. What is the new knowledge of the study?

Reply: Thank you for this observation. After reviewed the relevant literature, we found that few studies had reported the genetic alterations of m-PM. The expression of specific oncogenes and binding proteins may facilitate the detachment of tumor cells from the primary site and subsequent implantation and proliferation of CRC cells in the peritoneal

cavity. Therefore, a reliable and integrated prediction model is needed to evaluate the risk of developing m-PM and improve the management of high-risk patients. Our study points out that BRAF mutation and MSI-H are independent risk factors to predict the occurrence of m-PM. We think this may add new knowledge to this topic.

6. Please recommend to the readers "How to apply this knowledge?

   Reply: Thank you for this suggestion. In this study, we used LASSO regression analysis to assess the impact of 23 clinical variables on the risk of developing m-PM following CRC surgery. Among the 23 clinical variables, 6 risk factors were screened out by LASSO regression analysis. Multiple logistic regression further confirmed that right colon cancer, pT4, histological types of mucinous adenocarcinoma and signet-ring cell carcinoma, elevated CA125, BRAF mutation, and MSI-H were independent risk factors for m-PM in CRC. We evaluated the scores of all patients and divided them into two subgroups: low-risk group (risk score ≤ 168) and high-risk group (risk score > 168). We think that patients in high-risk group should be given special consideration and examined using more aggressive imaging modalities mentioned in this study. Then, if a positive result is suspected on the targeted examinations, we could perform second-look surgery using laparoscope to evaluate the extent of disease and obtain pathological evidence. Finally, if m-PM is diagnosed, surgeons are supposed to estimate the PCI score and decide whether aggressive treatment including CRS plus HIPEC should be performed in targeted patient. Thank you again for your kind suggestion.

Reviewer #2: The authors have clinical datum of 965 patients were enrolled in this study from Second Hospital of Jilin University, between January 1, 2014 and January 31, 2019. The patients were randomly divided into training and validation cohorts at a ratio of 2:1. Multivariate logistic regression was used to

verify the selected variables and to develop the predictive nomogram model. The nomogram included 7 predictors: emergency operation, tumor site, histological type, pathological T stage, CA125, BRAF mutation and MSI status. The model achieved a good prediction accuracy on both the training and validation datasets. Minor issues: The emergency cases (obstructed or perforated) should be excluded from the analysis for especially perforation is considered as a distant metastasis because the peritoneal spread risk increases which is known fact. Otherwise the manuscript is well written and professionally presented.

Response to reviewer #2: We are very grateful for your affirmation and professional advice. We have added emergency surgery into the exclusion criteria. Therefore, patients undergoing emergency surgery were excluded from this study. The new model included 6 predictors: tumor site, histological type, pathological T stage, CA125, BRAF mutation and MSI status. The new model also achieved a good prediction accuracy on both the training and validation cohorts. In addition, we deleted the analysis of emergency surgery in the discussion section. Thank you again for your valuable comments.

Yours sincerely,
Bo Ban