Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of my manuscript titled Nomogram for Predicting Pathological Complete Response to Neoadjuvant Chemotherapy in Patients with Advanced Gastric Cancer (manuscript NO:53005) to *World Journal of Gastroenterology*. We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect the suggestions provided by the reviewers. All changes have been highlighted in yellow in the revised manuscript. We have also added point-to-point response to the reviewer's comment along with this cover letter. In addition to the revision, the manuscript has been carefully formatted according to the guideline of WJG.

We hope that the revised manuscript will be deemed suitable for publication in *World Journal of Gastroenterology*. We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

Junsheng Peng

Point-by-point response to the reviewers' comments

Comment 1: *Preoperative chemotherapy has been proved to improve survival outcomes only when it was given as part of perioperative chemotherapy. What about postoperative adjuvant chemotherapy in this patient group?*

Response: The reviewer pointed out an important point of this research. We very much agree with this comment. But unfortunately, we don't have sufficient data to analyze the survival impact of the preoperative or postoperative chemotherapy. Nevertheless, we have added a Table 4 in page 28 depicting the postoperative adjuvant chemotherapy received by this patient group. It's also elucidated in page 9, line 26- page 10, line 4. The statements are added below for your perusal:

Table 4. Postoperative adjuvant chemotherapy

	n=208	%
Platin-based doublet regimen	126	60.6
FOLFOX	75	36.1
SOX	48	23.1
XELOX	3	1.4
Taxanes contained regimen	42	20.2
mFLOT	15	7.2
Docetaxel plus fluorouracil	25	12.0
Docetaxel plus S-1 capsule	2	1.0
Monotherapy	22	10.6
S-1 capsule	13	6.3
Capecitabine	9	4.3
No adjuvant chemotherapy	18	8.7

"92% (191/208) of patients received postoperative adjuvant chemotherapy. Most patients (126/208,60.6%) received platin-based doublet regimen such as FOLFOX or its analog (SOX, XELOX). Although mFLOT serve as the mainstream regimen (122/208,58.7%) in NAC, only a small portion of patients (15/208,7.2%) accepted mFLOT as adjuvant chemotherapy because of the

rather intolerable toxicity. Other regimen includes taxanes contained doublet regimen (27/208,13.0%) and oral agents such as S-1 capsule or capecitabine (22/208,10.6%)."

Comment 2: *Data regarding peritoneal washing cytology test was not described.*

Response: For the reviewer's information, the reason that peritoneal washing cytology test was not described in this manuscript is due to the fact that it is not a clinical routine in our center. However, we did conduct this test in a minority of the patients (n=3), and all results came out negative. We have now included the above statements in page 9, line 16-17 in the revised manuscript.

Comment 3: *The authors should describe the data regarding adverse events during NAC and postoperative complications including mortality.*

Response: Per the reviewer's request, we have now described the data regarding hematological toxicities during NAC and postoperative complications including mortality (please see revised Table 2 and Table 3, page 26, 27 and result section, page 9, line 8-25). But due to the incomplete documentation, data regarding non-hematological toxicities is not retrievable. The additions are also added below for your perusal:

Table 2. Hematological toxicity of neoadjuvant chemotherapy

	mFLOT (n=122)		FOLFOX SOX/XELOX (n=75)		Other † (n=11)	
Grade	3	4	3	4	3	4
Anemia	41	15	18	9	6	3
Neutropenia	24	26	25	5	5	1
Febrile-Neutropenia	6	0	1	0	0	0
Thrombocytopenia	8	4	8	0	0	5

† *Other Regimen includes 10 cases of Docetaxel plus fluorouracil and 1 case of*

Docetaxel monotherapy.

Table 3. Postoperative complication and mortality

	Total (n=208)	Non-pCR (n=181)	pCR (n=27)	P
Any complication	44	41	3	0.25
Abdominal abscess	31	28	3	0.60
Anastomotic leakage	10	9	1	0.08
Duodenal stump leakage	2	1	1	0.13
Other leakage †	8	7	1	0.97
Bleeding	4	4	0	0.44
Intra-abdominal bleeding	3	3	0	0.50
Anastomotic bleeding	1	1	0	0.70
Pneumonia	12	10	2	0.13
pancreatic fistula	3	2	1	0.30
obstruction or ileus	3	2	1	0.30
Diarrhea	2	2	0	0.59
Diabetes	1	0	1	0.01
Reoperation	2	1	1	0.13
Death before discharge	1	1	0	0.70

† *Other leakage: Includes esophagojejunal anastomotic leakage, gastrojejunal anastomotic leakage and intestinal anastomotic leakage.*

"The most common grade 3/4 hematological toxicities were anemia (92/208, 44.2 %) and neutropenia (86, 41.3 %). The incidence rates of grade 3/4 thrombocytopenia and febrile-neutropenia were 12.0%(25/208) and 3.7%(7/208) , respectively. Grade 3/4 hematological toxicities were more common is docetaxel contained regimens than oxaliplatin-based doublet regimens in terms of anemia (48.9% vs 36%) and febrile-neutropenia (4.5% vs 1.3%), but the differences is not statistically significant.

Postoperative complications were observed in 44 patients (21.2%). The incidence rate was not statistically different between pCR (41/181,22.7%) and Non-pCR group (3/27,11.1%). Abdominal abscess is the most frequent complication in both groups and were all resolved by non-surgical management such as percutaous centesis drainage, enteral nutrition support and antibiotic therapy. Two patients underwent reoperation due to intestinal obstruction. One patient died of progressive pneumonia 6 weeks after surgery in intensive care unit."

Comment 4: *The authors described that they established a nomogram with satisfactory predictive power of pCR. However, it is not so convincing to say that the predictive power of the model is satisfactory by applying the model to the group that made the predictive model itself. The authors should split the patients into a training set and a validation set to validate the predictive model.*

Response: We appreciate the reviewer's concern on this matter. We totally agree with the reviewer that the validation of the predictive model would be better if the patients were to be divided into training and validation set. We did consider splitting the patients into a training set and a validation set to performed an external validation. Unfortunately, there is not enough cases to allow us to do so. If we split the cohort in two, the cases would not be sufficient to build this nomogram. Therefore, as an alternative solution, we validated it internally with the bootstrap method, the same method used by other authors when the total case number is small[1-5].

A similar study was published on WJG in 2019, Ren *et al*. established a nomogram for predicting partial response to preoperative neoadjuvant treatments in patients with rectal cancer. 403 patients included in the study and bootstrap method was adopted to determine a C-index of 0.79, stating that the nomogram was accurate and effective.

An external cohort validation is indeed important. However, under the current condition of lacking sufficient cases, internal bootstrap method validation also

prove to be an effective alternative method[1-5].

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Sincerely,

Junsheng Peng

Point-by-point response to the reviewers' comments

Comment 1: *The number of patients who received postoperative adjuvant chemotherapy does not match the number obtained from the total number of patients and the number of patients who did not receive adjuvant chemotherapy.*

Response: To verify this point, we went through the tables and data again but failed to find any mismatch of numbers. As depicted in **Table 4**, of the 208 patients enrolled in our study, 18 received no post-operative adjuvant chemotherapy (highlight in grey at the tables below), 126 received platin-based doublet regimen (including FOLFOX, SOX and XELOX, highlighted in blue at the tables below) as post-operative adjuvant chemotherapy, 42 received taxanes contained regimen (including mFLOT, docetaxel plus fluorouracil and docetaxel plus S-1 capsule, highlighted in red at the tables below) and 22 received monotherapy regimen (including S-1 capsule and capecitabine, highlighted in green at the tables below), all add up to 208, same as the total number. We assumed that the reason why the reviewer raised this question is because of the confusing arrangement of data in the original **Table 4**, in which regimens were categorized into subgroups and the numbers of different regimens and subgroups are mixed together in the 2nd column:

Table 4. Postoperative adjuvant chemotherapy

	n=208	%
Platin-based doublet regimen	126	60.6
FOLFOX	75	36.1
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Capecitabine	9	4.3
No adjuvant chemotherapy	18	8.7

Abbreviation for FOLFOX, SOX, XELOX and mFLOT are listed in section MATERIALS AND METHODS

We apologize for the confusing description of our data. Thus, to avoid further confusion, we rearranged the numbers, removing the number of each subgroup.

Table 4. Postoperative adjuvant chemotherapy

	n=208	%
Platin-based doublet regimen		
FOLFOX	75	36.1
SOX	48	23.1
XELOX	3	1.4
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Capecitabine	9	4.3
No adjuvant chemotherapy	18	8.7

Abbreviation for FOLFOX, SOX, XELOX and mFLOT are listed in section MATERIALS AND METHODS

Comment 2: *In the revised Table 2 and 3, percent value should be added.*

Response: Per the reviewer's request, we have now added the percentage value for each data.

Table 2. Hematological toxicity of neoadjuvant chemotherapy

	mFLOT (n=122)		FOLFOX SOX/XELOX (n=75)		Other † (n=11)	
Grade	3	4	3	4	3	4
Anemia	41(33.6%)	15(12.3%)	18 (24%)	9 (12%)	6 (54.5%)	3 (27.3%)
Neutropenia	24(19.7%)	26(21.3%)	25(33.3%)	5 (6.7%)	5 (45.5%)	1 (9.1%)
Febrile-Neutropenia	6 (4.9%)	0	1 (1.3%)	0	0	0
Thrombocytopenia	8 (6.6%)	4 (3.3%)	8 (10.7%)	0	0	5 (45.5%)

† *Other Regimen includes 10 cases of Docetaxel plus fluorouracil and 1 case of Docetaxel monotherapy.*

Table 3. Postoperative complication and mortality

	Total (n=208)	Non-pCR (n=181)	pCR (n=27)	P
Any complication	44 (21.2%)	41 (22.7%)	3 (11.1%)	0.25
Abdominal abscess	31 (14.9%)	28 (15.5%)	3 (11.1%)	0.60
Anastomotic leakage	10 (4.8%)	9 (5%)	1 (3.7%)	0.08
Duodenal stump leakage	2 (1%)	1 (0.6%)	1 (3.7%)	0.13
Other leakage †	8 (3.8%)	7 (3.9%)	1 (3.7%)	0.97
Bleeding	4 (1.9%)	4 (2.2%)	0	0.44
Intra-abdominal bleeding	3 (1.4%)	3 (1.7%)	0	0.50
Anastomotic bleeding	1 (0.5%)	1 (0.6%)	0	0.70
Pneumonia	12 (5.8%)	10 (5.5%)	2 (7.4%)	0.13
pancreatic fistula	3 (1.4%)	2 (1.1%)	1 (3.7%)	0.30
obstruction or ileus	3 (1.4%)	2 (1.1%)	1 (3.7%)	0.30
Diarrhea	2 (1%)	2 (1.1%)	0 (0%)	0.59
Diabetes	1 (0.5%)	0	1 (3.7%)	0.01
Reoperation	2 (1%)	1 (0.6%)	1 (3.7%)	0.13
Death before discharge	1 (0.5%)	1 (0.6%)	0	0.70

† *Other leakage: Includes esophagojejunal anastomotic leakage, gastrojejunal anastomotic leakage and intestinal anastomotic leakage.*

Comment 3: *"Table 4" should be corrected to "Table 3" in Page 9, Line 20.*

Response: We apologize for the overlook. "Table 4" in Page 9, Line 20 have now been corrected to "Table 3" (Page 9, Line 21). The correction is highlighted in the manuscript.