

## **1、 Answers to editor:**

1. We have added ARTICLE HIGHLIGHT in our manuscript based on the requirements.
2. Figure 1 was generated using VISIO software. Here we provide the editable version in word form. Text could be easily edited by double clicking. Please make sure that VISIO was installed in your computer.
3. We have provided original figure 2 with editable text in a PPT document and submitted it in the system
4. Figure 3 including line drawings and text was automatically generated using R software. We have put it in a PPT document and changed the text into editable form.
5. Figure 4 was generated using R software. We are sorry that numbers within the figure can neither be changed nor edited. We have tried our best to change part of the text into editable form in PPT document.
6. We have added explanations of abbreviation in table legend for table 1 and 2. Thank you.
7. We replaced “multiple logistic regression” with “multivariable logistic regression” which was considered to be a more professional term.

## **2、 answers to all the reviewers:**

### **To the first reviewer:**

1. The Methods do not clearly explain the randomization method, e.g. what is meant by a “training set” and what is a “validation set”.

Answer: When developing a model, data is usually divided into two sets. Training set is used to establish the model while testing set is used to evaluate the predicting ability of the model as well as the prognostic accuracy. We found it more precise to use the term “testing set” here instead of “validation set”. Thus, we revised our manuscript accordingly (See Statistical analysis section).

Besides, all cases were allocated a random number generated by SPSS. The range of random numbers was set from 0 to 100. Cases with numbers ranging from 0 to 80 were assigned to the training set, and those with numbers ranging from 80.0001 to 100 were assigned to the testing set. Our random seed was 666 as mentioned in our manuscript. The statistical analysis could easily be repeated using the same random seed. This is the most commonly used statistical method, so we find it unnecessary to describe it in detail.

2. Furthermore, the objectives clearly state that the risk for surgery is estimated after one year from diagnosis, but in the analysis were included patient with previous resections associated with Crohn's disease and perianal surgery. How do you explain their inclusion?

Answer: Crohn's disease is a chronic intestinal inflammatory disease facing great difficulties in diagnosis. A great number of patients have undergone intestinal surgery such as appendectomy or perianal surgery for the sake of perianal abscess or fistula before diagnosis. Therefore, previous surgery is not the exclusion criteria. Further, according to the results of our research, previous surgery which manifested progressive type of CD, was a confirmed factor associated with early surgery.

3. Ultrasound as a method of diagnosis of Crohn's disease is highly dependent on the training and experience of the operator. Was the bowel UTS performed by well-trained operators?

Answer: Our clinical center is the biggest IBD center in China, with a strong team composed of professional gastroenterologists, pathologists, radiologists as well as gastrointestinal surgeons. The bowel ultrasound of IBD patients was performed by fixed, well-trained and professional gastroenterologists. Therefore, the results are credible and comparable. Thank you for your advice, we have added details on the ultrasound operators in our manuscript (see Definition section).

4. Exclusive enteral nutrition (EEN) has proven to be effective in the first manifestation of the disease, especially in small bowel affection. In your work, the effect of EEN in disease complications was examined. It is not stated whether all patients with complications used EEN, or only part of them. The characteristics of patients who have been on EEN should be stated.

Answer: Since EEN is effective in promoting fistula closure and reducing the size of abscess, most of the patients with complications such as intestinal fistula, abdominal abscess and stricture would be firstly given EEN applications. However, surgery should be launched without hesitation on a minor part of patients with complications such as uncontrolled intestinal bleeding and severe peritonitis due to perforation. Therefore, not all the patients with complications should receive EEN application. Special group of CD patients including pregnant women and children might need EEN treatment even though they did not develop complications. Our study showed that 230 (22.95%) patients had received exclusive enteral nutrition treatment during the follow-up period, 76.10% (n=175) of which had complications including intestinal fistula, abdominal abscess, and stricture. Thank you for your suggestions, we have added detailed characteristics of patients who have been on EEN (see Discussion Section).

5. Relevant literature is cited in the paper, but abbreviations of the journals title are not adequately written.

Answer: Literatures in our manuscript were edited using endnote software according the requirements of WJG. We confirmed all the literature information were correct.

6. The numbers and explanations of the pictures should be written below, not above the picture.

Answer: Thank you for your advices. We have revised accordingly (See picture legend section).

**To the second reviewer:**

1. The rate of intestinal surgery at 1 year appears to be quite high (24.25%) and does not reflect the usual course of Crohn's disease (CD).

Answer: Thank you for raising this question which we have ignored to discuss about in the Discussion Section. According to recent cohort studies from Denmark and Canada, 13%, 21%, and 26% of the patients underwent surgical resections after 1, 5, and 10 years, respectively. The rate of intestinal surgery in our IBD center was high with reasons as follows: Firstly, our IBD center was the largest one in China with CD patients from nationwide, most of whom had various complications and did not respond to medical therapy. Besides, our center was particularly famous for gastrointestinal surgery, part of patients came to seek surgery treatment. We have added the above in Discussion Section.

2. While including factors in a model, a predictor can be included in multivariate analysis if it is important even if it doesn't have the desired p value on univariate analysis. Age at onset of disease should have been included in the multivariate analysis.

Answer: We can not agree with reviewer more. Actually, we have included factors which were core important in clinical practice such as age and disease location at diagnosis, both of which showed  $P < 0.05$  in univariate analysis though (Figure 1). We ran SPSS on forward stepwise method as mentioned in Statistical Analysis Section. However, results showed no changes in model which manifested that neither age nor location were the independent factors associated with early intestinal surgery (Figure 2).

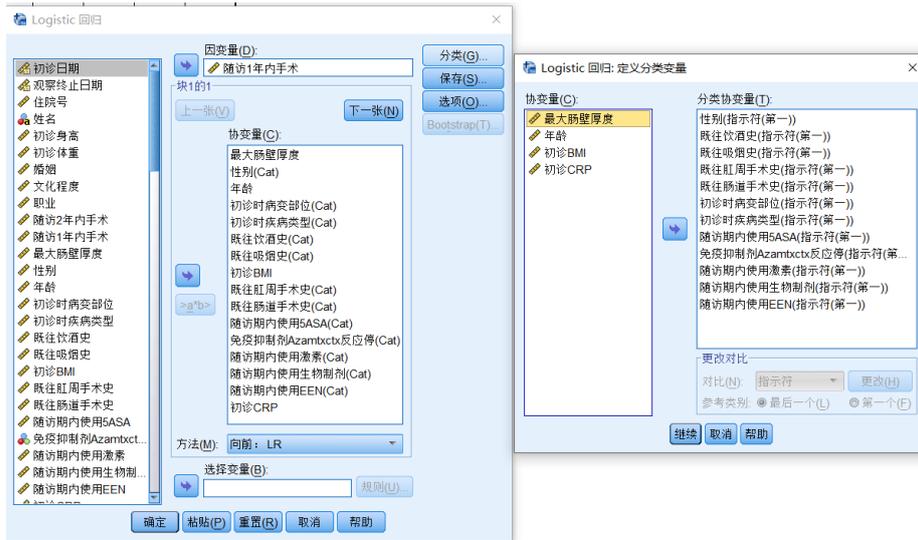


Figure 1 Factors we included in multivariate analysis.

		Variables in the Equation						95% C.I. for EXP(B)	
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1 <sup>a</sup>	初诊时疾病类型			137.970	2	.000			
	初诊时疾病类型(1)	1.779	.229	60.395	1	.000	5.926	3.783	9.283
	初诊时疾病类型(2)	2.577	.226	130.171	1	.000	13.152	8.448	20.475
	Constant	-2.258	.155	212.360	1	.000	.105		
Step 2 <sup>b</sup>	初诊时疾病类型			125.795	2	.000			
	初诊时疾病类型(1)	1.833	.250	53.653	1	.000	6.251	3.828	10.207
	初诊时疾病类型(2)	2.772	.255	117.930	1	.000	15.996	9.699	26.383
	既往肠道手术史(1)	2.005	.217	85.068	1	.000	7.429	4.851	11.376
	Constant	-3.386	.229	218.820	1	.000	.034		
Step 3 <sup>c</sup>	最大肠壁厚	.577	.070	68.081	1	.000	1.780	1.552	2.041
	初诊时疾病类型			123.274	2	.000			
	初诊时疾病类型(1)	2.083	.276	56.820	1	.000	8.031	4.672	13.805
	初诊时疾病类型(2)	3.074	.286	115.742	1	.000	21.634	12.356	37.876
	既往肠道手术史(1)	2.193	.240	83.728	1	.000	8.959	5.601	14.329
Step 4 <sup>d</sup>	Constant	-5.819	.435	179.184	1	.000	.003		
	最大肠壁厚	.627	.075	69.566	1	.000	1.873	1.616	2.170
	初诊时疾病类型			85.318	2	.000			
	初诊时疾病类型(1)	1.898	.300	40.107	1	.000	6.670	3.707	12.000
	初诊时疾病类型(2)	2.686	.302	79.029	1	.000	14.679	8.119	26.542
	既往肛周手术史(1)	1.877	.247	57.598	1	.000	6.536	4.025	10.615
Step 5 <sup>e</sup>	既往肠道手术史(1)	2.235	.256	76.337	1	.000	9.342	5.659	15.422
	Constant	-6.634	.498	177.637	1	.000	.001		
	最大肠壁厚	.672	.080	70.250	1	.000	1.958	1.673	2.291
	初诊时疾病类型			94.353	2	.000			
	初诊时疾病类型(1)	1.977	.314	39.650	1	.000	7.222	3.903	13.364
	初诊时疾病类型(2)	3.131	.332	88.888	1	.000	22.903	11.945	43.913
	既往肛周手术史(1)	2.148	.268	64.020	1	.000	8.563	5.060	14.491
Step 6 <sup>f</sup>	既往肠道手术史(1)	2.120	.264	64.527	1	.000	8.333	4.968	13.979
	随访期内使用EEN(1)	-2.033	.381	28.474	1	.000	.131	.062	.276
	Constant	-6.653	.523	161.526	1	.000	.001		
	最大肠壁厚	.669	.082	65.959	1	.000	1.953	1.661	2.295
	初诊时疾病类型			87.857	2	.000			
	初诊时疾病类型(1)	1.961	.324	36.705	1	.000	7.107	3.768	13.404
Step 6 <sup>f</sup>	初诊时疾病类型(2)	3.069	.337	82.946	1	.000	21.512	11.114	41.638
	既往吸烟史(1)	1.479	.320	21.363	1	.000	4.389	2.344	8.219
	既往肛周手术史(1)	2.156	.275	61.316	1	.000	8.636	5.034	14.813
	既往肠道手术史(1)	2.115	.271	60.966	1	.000	8.293	4.876	14.102
	随访期内使用EEN(1)	-1.909	.386	24.429	1	.000	.148	.070	.316
	Constant	-6.929	.549	159.394	1	.000	.001		

Step 7 <sup>a</sup>	最大肠壁厚度	.675	.085	63.752	1	.000	1.964	1.664	2.318
	初诊时疾病类型			74.139	2	.000			
	初诊时疾病类型(1)	1.913	.332	33.239	1	.000	6.775	3.535	12.984
	初诊时疾病类型(2)	2.851	.344	68.725	1	.000	17.309	8.821	33.965
	既往吸烟史(1)	1.372	.328	17.471	1	.000	3.945	2.073	7.508
	既往肛周手术史(1)	2.125	.280	57.560	1	.000	8.372	4.836	14.496
	既往肠道手术史(1)	2.160	.279	59.869	1	.000	8.673	5.018	14.990
	随访期内使用生物制剂(1)	-1.181	.283	17.407	1	.000	.307	.176	.535
	随访期内使用EEN(1)	-2.045	.394	26.949	1	.000	.129	.060	.280
	Constant	-6.407	.554	133.694	1	.000	.002		
Step 8 <sup>b</sup>	最大肠壁厚度	.677	.085	62.780	1	.000	1.968	1.665	2.327
	初诊时疾病类型			65.995	2	.000			
	初诊时疾病类型(1)	1.902	.338	31.718	1	.000	6.700	3.456	12.989
	初诊时疾病类型(2)	2.707	.351	59.575	1	.000	14.991	7.538	29.813
	既往吸烟史(1)	1.369	.331	17.127	1	.000	3.931	2.056	7.517
	既往肛周手术史(1)	2.254	.292	59.416	1	.000	9.529	5.372	16.905
	既往肠道手术史(1)	2.124	.284	55.810	1	.000	8.363	4.791	14.601
	随访期内使用生物制剂(1)	-1.281	.294	19.018	1	.000	.278	.156	.494
	随访期内使用EEN(1)	-2.348	.422	30.936	1	.000	.096	.042	.219
	初诊CRP	.025	.007	13.866	1	.000	1.025	1.012	1.038
Constant	-6.818	.579	138.811	1	.000	.001			
Step 9 <sup>i</sup>	最大肠壁厚度	.676	.086	61.475	1	.000	1.965	1.660	2.327
	初诊时疾病类型			63.640	2	.000			
	初诊时疾病类型(1)	1.901	.340	31.264	1	.000	6.693	3.437	13.032
	初诊时疾病类型(2)	2.668	.353	57.011	1	.000	14.405	7.208	28.790
	既往吸烟史(1)	1.419	.334	18.085	1	.000	4.135	2.149	7.953
	初诊BMI	-.136	.053	6.576	1	.010	.873	.786	.968
	既往肛周手术史(1)	2.249	.295	58.072	1	.000	9.483	5.317	16.912
	既往肠道手术史(1)	2.185	.289	57.182	1	.000	8.887	5.045	15.656
	随访期内使用生物制剂(1)	-1.333	.301	19.556	1	.000	.264	.146	.476
	随访期内使用EEN(1)	-2.423	.427	32.166	1	.000	.089	.038	.205
初诊CRP	.022	.007	11.464	1	.001	1.022	1.009	1.036	
Constant	-4.276	1.108	14.882	1	.000	.014			

a. Variable(s) entered on step 1: 初诊时疾病类型.

b. Variable(s) entered on step 2: 既往肠道手术史.

c. Variable(s) entered on step 3: 最大肠壁厚度.

d. Variable(s) entered on step 4: 既往肛周手术史.

e. Variable(s) entered on step 5: 随访期内使用EEN.

f. Variable(s) entered on step 6: 既往吸烟史.

g. Variable(s) entered on step 7: 随访期内使用生物制剂.

h. Variable(s) entered on step 8: 初诊CRP.

i. Variable(s) entered on step 9: 初诊BMI.

Figure 2 Results of SPSS on forward stepwise method.

### 3. What duration of biological therapy or exclusive enteral nutrition was considered as cut-off for inclusion in this study?

Answer: We feel confused about this question. Does the reviewer want to ask at least how long the course of biological and EEN treatments should be included in our study? Patients who have ever received biological therapy no matter in the induction or remission maintenance period were identified as receiving biological therapy. Patients who received EEN for at least one month were identified as undergoing EEN treatment.

### 4. Among the 1002 patients included, were data on all parameters available in each of them?

Answer: As what have been mentioned in our manuscript, 1203 patients were diagnosed as

Crohn's disease and 201 (16.7%) patients were excluded for the sake of incomplete data (n=42, 20.9%), loss to follow-up (n=156, 77.6%), or death (n=3, 1.5%). In this research, a total of 1002 eligible patients with complete data were enrolled. Data on all parameters were available for all the 1002 patients.

**5. How was the site for estimating bowel wall thickness determined, and in what proportion the evaluation was suboptimal?**

Answer: Bowel wall thickness (BWT) was scanned in the whole intestinal tract and measured in both the longitudinal and transverse slices. All the CD patients will have intestinal ultrasound examination according to standard operation procedure in our IBD center. We have added the site for bowel ultrasound estimation in our manuscript (See definition section).

**6. The performance of the model in the validation set showed less than 70% sensitivity and the nomogram appears complex to use. Thus limits the clinical utility of this model.**

Answer: Testing set included only 20% of all the data. Relatively small amount of cases would lead to bias to some extent and could not represent the model. In the model established with training set data, the sensitivity was higher than 75% and the specificity was even higher than 95%, which showed an ideal predictable ability of this model. A nomogram was a tool to facilitate convenient use in clinical practice. Probability of early intestinal surgery was easily obtained by calculating the total number of points and matching vertically downward to the risk of surgery at 1 year. Risk of surgery would be obtained just by simple addition and nomogram referring.

**To the third reviewer:**

**Language edition required**

Answer: Thanks to Editage, a communication offers professional English language editing, We have language edited in the revised manuscript.

**Please do not hesitate to contact us if any more information is needed. Thank you.**