

Dr. Jin-Lei Wang,
Company Editor-in-Chief
World Journal of Clinical Cases

Ms. No. 70370

Title. Predictive value of alarm symptoms in Rome IV irritable bowel syndrome: A multicenter cross-sectional study

Dear Dr. Jin-Lei Wang,

Thank you for your instructive comments on our manuscript. We have carefully revised the manuscript following your and the reviewers' suggestions and comments. The detailed responses to the comments are as follows:

Reviewer #1: Specific Comments to Authors: A well-focused study of a disease that has a high prevalence in the general population. The conclusions are not particularly innovative however it should be considered that strengthening the evidence of which symptoms are red flag of underlying organic pathologies in the population for suspected IBS is in any case necessary.

Response: Thank you very much for the positive comments. As the reviewer said, IBS is a very common functional bowel disease. The latest study based on the Rome IV criteria shows that the prevalence of IBS is 4.6%^[1]. In clinical practice, medical workers often adopt the "exclusion diagnosis strategy" in diagnosing IBS (that is, to perfect various examinations). However, IBS management guidelines advocate a "positive diagnosis strategy" for suspected IBS patients^[2,3]. Studies have shown that the available biomarkers and psychological assessment measures have limited predictive value for IBS^[4]. At the same time, too many diagnostic tests and uncertain clinical diagnosis will aggravate the emotional disorder of patients. This will not only increase the burden on patients and society but also make patients lose confidence in doctors and form a vicious circle in the long run. However, the symptoms of IBS overlap with a variety of organic bowel diseases and missed diagnosis will lead to serious consequences^[5]. Therefore, evaluating the predictive value of alarm symptoms for suspected IBS patients, determining the risk of organic bowel disease more accurately, and giving necessary examinations is of great significance for the correct diagnosis of IBS.

The results of previous relevant studies are inconsistent, and the value of alarm symptoms needs to be further discussed^[6-8]. The Rome IV criteria have made great changes on the basis of Rome III. At present, there is no relevant research based on the Rome IV criteria^[9]. This study can provide more reference data for the clinical diagnosis of IBS. Subsequently, we hope to further build a simple, practical and efficient IBS diagnosis model by collecting large-scale and high-quality multicenter data.

Reviewer #2: Specific Comments to Authors: Interesting study with accurate methodology. The findings might not be surprising, but science needs always to check what we observe on a regular basis and measure it, in order to be able to predict in the future similar findings. Your study shows and ponderates the relationship between IBS and its risk factors, standarized in the main clinical guidelines. It interesting to see how Anemia + Fecal occult blood + Unintended weight loss get a 100% of PPV of organic disease. It would be interesting to stratify the weight loss in different levels (as shown in the table), or the severity of the anemia. However, I find it a well-structured interesting study. Congratulations

Response: We are very grateful for the reviewer's positive comments and valuable suggestions. Indeed, clinical guidelines and expert consensus emphasize the importance of evaluating alarm symptoms for the

diagnosis of IBS, and the findings of this study are also consistent with some previous conclusions^[6,8]. However, previous similar studies have focused on the Manning criteria or Rome I, II and III criteria, and there is no relevant research based on the Rome IV criteria. The contents of alarm symptoms in different periods and regions are different, and the results of previous studies are also different^[7,10,11]. The predictive value of alarm symptoms based on Rome IV for the risk of organic bowel disease in suspected IBS patients needs to be further studied.

We found that anemia, fecal occult blood and unintended weight loss have high predictive value for organic diseases. Among them, unintended weight loss was divided into different levels. We originally intended to classify the severity of anemia. However, some patients had routine blood examinations in other hospitals within the last 6 months who claimed to have anemia and failed to provide examination reports. That is, specific data on red blood cells and hemoglobin cannot be obtained, and anemia cannot be quantitatively evaluated. We will make further improvements in future research and thank the reviewer for the valuable suggestions.

Science editor: The manuscript reported a study of the predictive value of alarm symptoms in Rome IV irritable bowel syndrome. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario.

Response: Thanks for the editor's positive comments. This study is a multicenter cross-sectional study. The researchers did not apply additional intervention, and the results are more in line with the actual clinical situation. The purpose of this study is to provide relevant data based on the Rome IV criteria and promote scientific research on IBS. Evaluating the value of alarm symptoms provides guidance for the clinical evaluation of the risk of organic diseases in suspected IBS patients and the correct diagnosis of IBS.

Nevertheless, there are a number of points that may deserve some revisions. 1. The author has collected a large number of data for analysis, but there is a lack of multicenter data, and the analysis means are relatively simple, such as stratified research according to age, gender, and psychological state, and formulating diagnostic prediction model?

Response: Thanks for the questions and valuable suggestions for improvement. As the editor said, the sample size of this study is relatively large, and a total of 730 subjects are enrolled. This multicenter study was conducted at three academic urban tertiary care centers, namely the Second Affiliated Hospital of Xi'an Jiaotong University, Tangdu Hospital of Air Force Medical University and the Affiliated Hospital of Northwest University (Xi'an No.3 Hospital) (see lines 1-5 in the first paragraph of the Materials and Methods section of the manuscript). However, the three centers are all the tertiary centers in Xi'an, lacking data from primary care units and multiple regions. We intend to continue to collect large-scale, high-quality and multiregional data and further formulate a simple, practical and efficient IBS diagnosis model.

We also thought about doing hierarchical analysis. However, considering that the onset age > 50 years is one of the alarm symptoms, it has not been done. According to suggestions of the editor, multivariate logistic analysis were performed in patients with age ≤50 years and >50 years. The results showed that anemia [odds ratio (OR) 3.915 (95% confidence interval (CI) 1.365-11.226), $P=0.011$], fecal occult blood [OR 2.795 (95% CI 1.131-6.904), $P=0.026$] and exercise time ≥ 1 h/d [OR 0.063 (95% CI 0.008-0.521), $P=0.010$] were independently associated with organic diseases among patients with age >50 years. The prediction model was as follows: $-2.771 \times \text{exercise time} \geq 1 \text{ h/d} + 1.365 \times \text{anemia} + 1.028 \times \text{fecal occult blood}$ (see Table 1 below for details); For people aged ≤50 years, female sex [OR 0.227 (95% CI 0.096-0.539), $P=0.001$] and unintended weight loss [OR 5.234 (95% CI 2.205-12.423), $P<0.001$] were independently associated with organic

diseases. The corresponding prediction model was: $-1.482 \times \text{female sex} + 1.655 \times \text{unintended weight loss} < 2.5\text{kg}$ (see Table 2 below for details). From the results, we can see that there are great differences in risk factors between the two age groups, but when the stratified results are superimposed together, they are almost consistent with the non stratified results. The combined data showed that age was not an independent risk factor. This indicates that there is a certain correlation between age and organic diseases, but the correlation may not be strong enough to cause statistical difference.

Stratified analysis was performed according to gender. The results showed that for female patients, age [OR 3.320 (95% CI 1.345-8.198), $P=0.009$] and fecal occult blood [OR 4.452 (95% CI 1.805-10.981), $P=0.001$] were independently associated with organic diseases. The corresponding prediction model was: $1.200 \times \text{onset age} > 50 \text{ years} + 1.493 \times \text{fecal occult blood}$ (see Table 3 below for details); For male patients, age [OR 0.420 (95% CI 0.198-0.892), $P=0.024$], rectal bleeding [OR 2.077 (95% CI 1.036-4.164), $P=0.039$], unintended weight loss $< 2.5\text{kg}$ [OR 3.299 (95% CI 1.439-7.563), $P=0.005$] and unintended weight loss $\geq 7.5\text{kg}$ [OR 17.496 (95% CI 2.083-146.951), $P=0.008$] were independently associated with organic diseases. The prediction model was shown as follows: $-0.868 \times \text{onset age} > 50 \text{ years} + 1.194 \times \text{unintended weight loss} < 2.5\text{kg} + 2.862 \times \text{unintended weight loss} \geq 7.5\text{kg} + 0.731 \times \text{rectal bleeding}$ (see Table 4 below for details). From the results, we can see that there are also great differences in risk factors among different gender groups. The combined data showed that gender was an independent risk factor, which may be related to the differences after stratification.

As for the psychological state, since the psychological self-rating scale (SAS, SDS) must be completed by the patients themselves, we do not require some older or less educated patients must to complete the assessment. In addition, some patients refused to fill in or the information was incomplete. Finally, we only included the psychological assessment results of 328 patients (see lines 3-5 in the first paragraph of the Results section of the manuscript). Therefore, we only included the data of 328 patients in the hierarchical analysis. The results showed that for those with psychological disorders (anxiety, depression or both), spicy food [OR 10.847 (95% CI 1.305-90.199), $P=0.027$], unintended weight loss $< 2.5\text{kg}$ [OR 21.216 (95% CI 3.030-148.580), $P=0.002$], unintended weight loss 2.5-5.0kg [OR 11.333 (95% CI 1.132-113.420), $P=0.039$] and anemia [OR 52.833 (95% CI 6.817-409.455), $P<0.001$] were independently associated with organic diseases. The prediction model was: $2.384 \times \text{spicy food} + 3.055 \times \text{unintended weight loss} < 2.5\text{kg} + 2.428 \times \text{unintended weight loss} 2.5-5.0\text{kg} + 3.967 \times \text{anemia}$ (see Table 5 below for details); For those without psychological disorders, fecal occult blood [OR 3.869 (95% CI 1.460-10.258), $P=0.007$] and unintended weight loss $< 2.5\text{kg}$ [OR 3.621 (95% CI 1.295-10.126), $P=0.014$] were independently associated with organic diseases. The prediction model was: $1.353 \times \text{fecal occult blood} + 1.287 \times \text{unintended weight loss} < 2.5\text{kg}$ (see Table 6 below for details). The results showed that there were differences between the two groups. This may require a larger sample size to verify because there is less data after stratification.

As mentioned earlier, the study was conducted in three academic urban tertiary care centers and was limited to Xi'an. The findings deserve further validation in primary care units in gastrointestinal clinics and in national multicenters. After stratification, the number of patients assigned to each group is less (especially psychological evaluation). Although the models were formed, their values should be further internally and externally validated. With the limited data, we decide to not show the results of the model currently. By collecting large-scale, high-quality and multi regional data, we will try to develop and validate the valuable prediction models in our future work.

Table 1 Multivariate analysis of risk factors associated with organic disease for patients >50 years old ($n=301$)¹

Characteristics	OR (95% CI)	P value	Partial regression
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			coefficient
Anemia (ref absence)	3.915 (1.365, 11.226)	0.011	1.365
Fecal occult blood (ref absence)	2.795 (1.131, 6.904)	0.026	1.028
Exercise time		0.063	
< half an hour/day	—	—	—
≥half an hour/day	0.485 (0.174, 1.355)	0.168	-0.723
≥1 hour/day	0.063 (0.008, 0.521)	0.010	-2.771
≥2 hours/day	0.679 (0.252, 1.832)	0.445	-0.387

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale and onset age, were included in the logistic regression analysis ("Forward: LR" method). *OR*: Odds ratio; *CI*: Confidence interval.

Table 2 Multivariate analysis of risk factors associated with organic disease for patients ≤50 years old (n=429)¹

Characteristics	OR (95% CI)	P value	Partial regression coefficient
Female (ref male)	0.227 (0.096, 0.539)	0.001	-1.482
Unintended weight loss (kg) ²		0.002	
Without	—	—	—
< 2.5	5.234 (2.205, 12.423)	<0.001	1.655
2.5-5.0	1.790 (0.378, 8.486)	0.463	0.582
5.0-7.5	1.511 (0.321, 7.110)	0.601	0.413
≥7.5	16.735 (0.829, 337.948)	0.066	2.817

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale and onset age, were included in the logistic regression analysis ("Forward: LR" method); ²Referred to weight loss in the last 3 months. *OR*: Odds ratio; *CI*: Confidence interval.

Table 3 Multivariate analysis of risk factors associated with organic disease for female patients (n=334)¹

Characteristics	OR (95% CI)	P value	Partial regression coefficient
Onset age > 50 years (ref ≤50 years)	3.320 (1.345, 8.198)	0.009	1.200
Fecal occult blood (ref absence)	4.452 (1.805, 10.981)	0.001	1.493

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale and gender, were included in the logistic regression analysis ("Forward: LR" method). *OR*: Odds ratio; *CI*: Confidence interval.

Table 4 Multivariate analysis of risk factors associated with organic disease for male patients (n=396)¹

Characteristics	OR (95% CI)	P value	Partial regression coefficient
Onset age > 50 years (ref ≤50 years)	0.420 (0.198, 0.892)	0.024	-0.868
History of gastrointestinal infection (ref absence)	0.224 (0.048, 1.048)	0.057	-1.496
Rectal bleeding (ref absence)	2.077 (1.036, 4.164)	0.039	0.731
Unintended weight loss (kg)		0.011	
Without	—	—	—

< 2.5	3.299 (1.439, 7.563)	0.005	1.194
2.5-5.0	1.315 (0.276, 6.266)	0.731	0.274
5.0-7.5	1.010 (0.214, 4.771)	0.990	0.010
≥7.5	17.496 (2.083, 146.951)	0.008	2.862

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale and gender, were included in the logistic regression analysis ("Forward: LR" method); ²Referred to weight loss in the last 3 months. *OR*: Odds ratio; *CI*: Confidence interval.

Table 5 Multivariate analysis of risk factors associated with organic disease for patients with psychological disorders (n=135)¹

Characteristics	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value	Partial regression coefficient
Spicy food (ref absence)	10.847 (1.305, 90.199)	0.027	2.384
Anemia (ref absence)	52.833 (6.817, 409.455)	<0.001	3.967
Unintended weight loss (kg) ²		0.032	
Without	—	—	—
< 2.5	21.216 (3.030, 148.580)	0.002	3.055
2.5-5.0	11.333 (1.132, 113.420)	0.039	2.428
5.0-7.5	2.567 (0.183, 35.988)	0.484	0.943
≥7.5	3.554 (0.077, 164.057)	0.517	1.268

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale, were included in the logistic regression analysis ("Forward: LR" method); ²Referred to weight loss in the last 3 months. *OR*: Odds ratio; *CI*: Confidence interval.

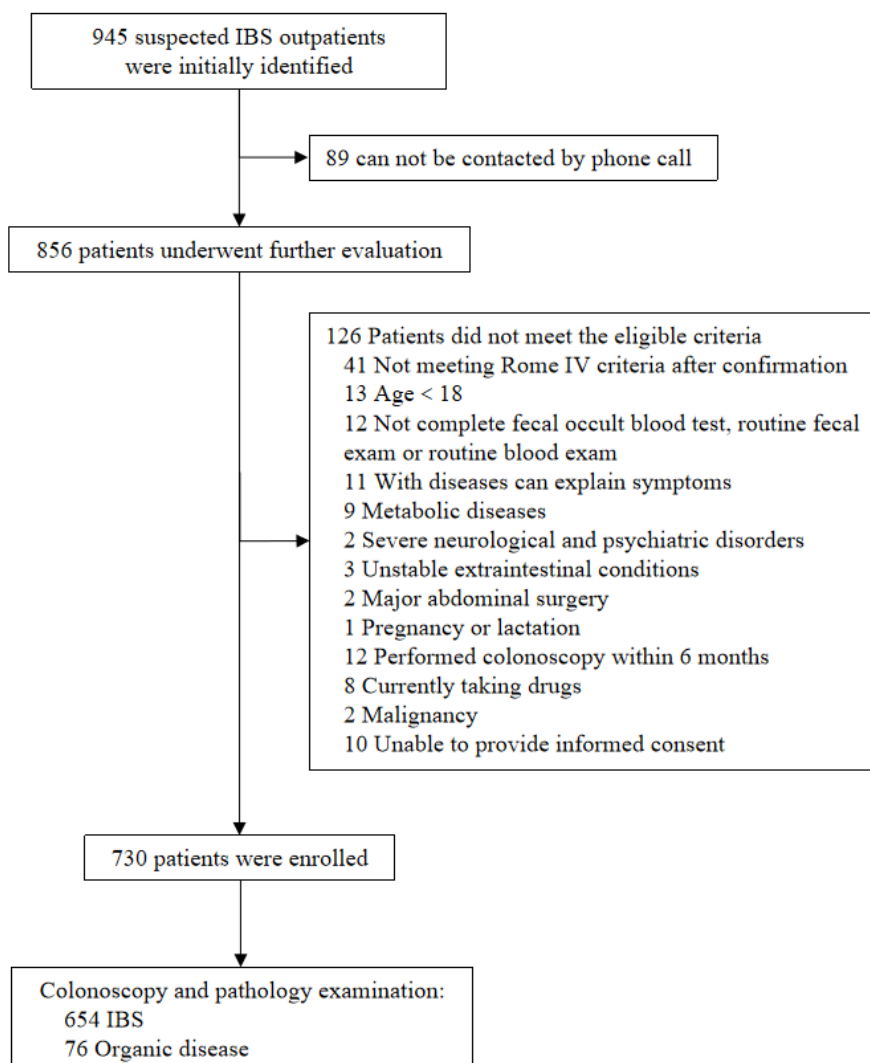
Table 6 Multivariate analysis of risk factors associated with organic disease for patients without psychological disorders (n=193)¹

Characteristics	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value	Partial regression coefficient
Fecal occult blood (ref absence)	3.869 (1.460, 10.258)	0.007	1.353
Unintended weight loss (kg) ²		0.194	
Without	—	—	—
< 2.5	3.621 (1.295, 10.126)	0.014	1.287
2.5-5.0	1.154 (0.132, 10.087)	0.897	0.144
5.0-7.5	1.561 (0.170, 14.341)	0.694	0.445
≥7.5	< 0.001	1.000	23.846

¹All factors in **Table 1** of the manuscript, except the psychological self-rating scale, were included in the logistic regression analysis ("Forward: LR" method); ²Referred to weight loss in the last 3 months. *OR*: Odds ratio; *CI*: Confidence interval.

2. The inclusion criteria for exclusion should be carefully described in Fig.1 Flow chart of the study, which is too simple at present.

Response: We thank the editor for the instructive suggestion. We have improved Fig.1 according to the advice, and the results are as follows:



Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Response: Thank you very much for the positive comments. We are glad to have the opportunity to revise the manuscript and hope that the article can be published smoothly. In accordance with the suggestions of the editor-in-chief and the guidance of the document "Guidelines for preparation of bitmaps, vector graphics, and tables in revised manuscripts (PDF)", we have modified the figures and tables of the manuscript accordingly (see the revised manuscript, "image file" and "table file" for details). At the same time, At the

same time, we also uploaded the relevant supporting documents of the foundation. See the document "Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s)" for details.

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