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Delayed Diagnosis is Associated with Early and Emergency Need for First Crohn's Disease-Related Intestinal Surgery

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Background: Increasing evidence suggests that delayed diagnosis in Crohn's disease is associated with a complicated disease course. The aim of this study was to explore the association between delayed diagnosis and the timing of the first Crohn's disease-related intestinal surgery.

Material/Methods: A retrospective study included 215 Crohn's disease patients with previous surgical history in the Department of General Surgery of Jinling Hospital, China, between January 2013 and March 2016. Data were collected on demographics, clinical characteristics, medication history, and operation history.





Results: The time from the first appearance of Crohn's disease-related symptoms to the first intestinal surgery in the delayed diagnosis group was obviously shorter than in the non-delayed diagnosis group (26.4±28.7 months vs. 42.6±58.4 months, respectively, $p=0.032$). Patients in the delayed diagnosis group tended to receive more ileal resections (47.8% vs. 26.4%, respectively, $p=0.002$) and less ileocecal resections (22.4% vs. 37.2%, respectively, $p=0.032$). More patients in the delayed diagnosis group received the first Crohn's disease-related intestinal surgery as an emergency one (20.9% vs. 4.7%, respectively, $p=0.001$).

Conclusions: Delayed diagnosis is associated with early and emergency need for the first Crohn's disease-related intestinal surgery.

MeSH Keywords: **Crohn Disease • Delayed Diagnosis • General Surgery • Intestines**

Abbreviations: **CD – Crohn's disease**

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Background

Crohn's disease (CD) is a chronic inflammatory bowel disease. In the long course of CD, intestinal surgery is almost inevitable, despite new diagnostic biomarkers [1,2] and new optimistic treatment approaches (like stem cell therapy [3]) increasingly applied in clinical practice. More than 80% of patients [4] with CD receive at least 1 intestinal surgery during their lifetime. Unfortunately, at present, CD cannot be fully cured through surgical interventions.

Increasing evidence suggests that delayed diagnosis of CD is associated with a complicated disease course, increased operation rate, and lower quality of life; this has been reported in different cohort, including cohorts from Switzerland [5], France [6], Italy [7], Romina [8], and Korea [9]. We recently reported our experience regarding the association between delayed diagnosis and increased rates of intestinal surgery in a Chinese cohort [10]. Recent research suggests that delayed diagnosis in a French cohort [11] of CD patients was associated with a greater risk of early major surgery.

However, the detailed effect of delayed diagnosis in CD patients, especially in a Chinese CD cohort, still needs to be explored. The specific type of surgery and the influence of delayed diagnosis also need to be determined. The aim of this study was to explore the association between delayed diagnosis and first CD-related intestinal surgery in a Chinese CD cohort.

Material and Methods

Patients

All patients were admitted to the Department of General Surgery of the Jinling Hospital, China, between March 2013 and June 2016. We included 342 patients who were definitively diagnosed with CD in this retrospective study.

The definite diagnosis of CD was based on a combination of comprehensive physical examinations, imaging examinations (such as computed tomography and magnetic resonance imaging), endoscopic examinations (including gastrointestinal endoscopy, gastrointestinal histopathological examination, and gastroenterography), blood examinations (including routine blood examination, erythrocyte sedimentation rate, C-reactive protein, and autoimmune-related antibodies), a detailed medical history, and other examinations.

There were 139 patients excluded from the study: 127 patients did not have a history of intestinal operation (including ileocecal resection, ileal resection, colectomy, ileostomy, and ileostomy), and 12 patients failed to provide complete

medical records. The diagnosis was histopathologically confirmed after surgery. After exclusions, 215 patients were enrolled in the study.

Ethics approval for the study was obtained from the Ethics Committee of Jinling Hospital.

Data collection

Patient data were collected from the electronic database of Jinling Hospital. Patients were contacted by telephone to obtain verbal informed consent. Data included the patient's sex (male or female), age at onset of first symptoms, age at diagnosis (according to Montreal classification [12]), initial disease location (according to Montreal classification), smoking history at diagnosis (yes or no), time of onset of first symptoms, time of first definitive diagnosis, time of first intestinal surgery, time of first visit to Jinling Hospital, medication history (yes or no, including sulfasalazine, mesalazine, corticosteroids, immunomodulators, and infliximab), and types of first CD-related intestinal surgery (yes or no, including ileocecal resection, ileal resection, colectomy, ileostomy, colostomy, and emergency surgery).

Emergency surgery was defined as the operation that needed to be performed in a short time (1 to 2 h); if not performed in a timely fashion, patients may have more serious or even life-threatening consequences. Emergency surgery was performed generally when hemorrhage, acute infection, or other acute abdomen occurred.

Patients enrolled who were diagnosed with CD at Jinling Hospital were diagnosed at an early stage; patients who were referred from other medical institutions had their previous medical records carefully reviewed, especially for the exact key study time points.

Definition of delayed diagnosis

The diagnostic interval was defined as the period from the first appearance of CD-related symptoms to the definitive diagnosis of CD. CD-related symptoms included abdominal pain, changes in bowel habits, abdominal distention, nausea and vomiting, and weight loss. The exact time of symptom occurrence, diagnosis, and the first intestinal surgery were obtained from the medical records.

The definition of diagnostic delay was the bottom quarter (75th to 100th percentile) of the diagnostic interval in CD patients, referring to the previous research of the Swiss inflammatory bowel disease cohort.

According to our results in a previous study [10], delayed diagnosis was defined as diagnostic interval of more than 34 months.

Table 1. Demographics and clinical characteristics of the study cohort according to delayed diagnosis.

Characteristic	The total	Non-delayed diagnosis group (n=148)	Delayed diagnosis group (n=67)	P
Male sex	153 (71.2%)	104 (70.3%)	49 (73.1%)	0.668
Age at onset of first symptoms (years)	29.8±11.1	29.8±11.0	29.9±11.3	0.915
Age at diagnosis (years)	32.7±12.0	30.5±11.1	37.5±12.5	0.000
A1 (≤16)	14 (6.5%)	14 (9.5%)	0	0.006
A2 (17-40)	150 (69.8%)	110 (74.3%)	40 (59.7%)	0.031
A3 (>40)	51 (23.7%)	24 (16.2%)	27 (40.3%)	0.000
Current smokers at diagnosis	37 (17.2%)	26 (17.6%)	11 (16.4%)	0.836
Initial disease location				
L1 (Terminal ileum)	95 (44.2%)	65 (43.9%)	30 (44.8%)	0.907
L2 (Colon)	35 (16.3%)	28 (18.9%)	7 (10.4%)	0.162
L3 (Ileocolon)	70 (32.6%)	47 (31.8%)	23 (34.3%)	0.709
L4 (Upper GI tract)	15 (7.0%)	8 (5.4%)	7 (10.4%)	0.246
From the first CD symptoms to the first intestinal surgery	37.6±51.5	42.6±58.4	26.4±28.7	0.032

GI – gastrointestinal; CD – Crohn’s disease. Results are given as the number and percent or the mean ±SD.

Therefore, the study cohort was divided into 2 groups: the diagnostic delay group (patients whose diagnostic interval was more than 34 months) and the non-diagnostic-delay group (patients whose diagnostic interval was less than 34 months). We compared the demographics and clinical characteristics of the 2 groups.

Statistical analysis

Statistical analysis was performed with SPSS Statistics software (Version 22.0.0; IBM, Armonk, NY). Classification data were available as the absolute frequency and percentage of the total. Parametric data were summarized as the mean ±SD. The interval from the first appearance of CD-related symptoms to first CD-related intestinal surgery was calculated using Kaplan-Meier methods and groups were compared with the log-rank test.

Quantitative data for the 2 groups were examined using the unpaired Student’s *t*-test. Categorical data were compared using the χ^2 test or Fisher’s exact test (in the case of a small sample size, $n < 5$ per group). A value of $p < 0.050$ was considered to indicate statistical significance.

Results

Demographics and clinical characteristics

The demographics and clinical characteristics of the study cohort are shown in Table 1. A total of 215 (62.9%) CD patients

with intestinal operation history were enrolled in the study. According to the definition of delayed diagnosis in our previous research, 148 patients were in the non-delayed diagnosis group and the other 67 patients were in the delayed diagnosis group. There were 153 male patients (71.2%), and 37 patients (17.2%) had smoking history when diagnosed.

The average age at onset of first symptoms was 29.8±11.1 years. The average age at diagnosis was 32.7±12.0 years. There were 150 patients (69.8%) diagnosed between 17 and 40 years of age, and 51 patients (23.7%) were diagnosed at over 40 years of age.

Using the Montreal classification for CD, the initial lesions of most patients were located in the terminal ileum (L1, 44.2%) and the ileocolon (L2, 32.6%).

The average period from the first appearance of CD-related symptoms to the first intestinal surgery was 37.6±51.5 months.

Comparing the non-delayed diagnosis group and the delayed diagnosis group, there were no statistically significant differences regarding sex, age at onset of first symptoms, smoking history at diagnosis, and initial disease location.

The age at diagnosis for the delayed diagnosis group (37.5±12.5 years) was significantly higher than in the non-delayed diagnosis group (30.5±11.1 years, $p < 0.001$).

Table 2. Medicine taking history of the study population from the time of Crohn's disease diagnosis.

Treatment	The total		Non-delayed diagnosis group (n=148)		Delayed diagnosis group (n=67)		P
Sulfasalazine	102	(47.4%)	74	(50.0%)	28	(41.8%)	0.264
Mesalazine	48	(22.3%)	34	(23.0%)	14	(20.9%)	0.735
Corticosteroids	55	(25.6%)	39	(26.4%)	16	(23.9%)	0.701
Immunomodulators	19	(8.8%)	14	(9.5%)	5	(7.5%)	0.797
Infliximab	3	(1.4%)	3	(2.0%)	0		0.554

As a patient may have undergone a combination of treatments, the percentage totals more than 100%.

Table 3. The first CD-related intestinal surgery of the study population according to delayed diagnosis.

Type of surgery	The total		Non-delayed diagnosis group (n=148)		Delayed diagnosis group (n=67)		P
Ileocecal resection	70	(32.6%)	55	(37.2%)	15	(22.4%)	0.032
Ileal resection	71	(33.0%)	39	(26.4%)	32	(47.8%)	0.002
Colectomy	90	(41.9%)	66	(44.6%)	24	(35.8%)	0.227
Ileostomy	19	(8.8%)	14	(9.5%)	5	(7.5%)	0.797
Colostomy	7	(3.3%)	3	(2.0%)	4	(6.0%)	0.208
Emergency surgery	21	(9.8%)	7	(4.7%)	14	(20.9%)	0.001

As a patient may have undergone a combination of surgeries, the percentage totals more than 100%.

The period from the first appearance of the CD-related symptoms to the first intestinal surgery in the delayed diagnosis group (26.4±28.7 months) was significantly shorter than in the non-delayed diagnosis group (42.6±58.4 months, $p=0.032$).

Medication history

As shown in Table 2, 102 patients (47.4%) received sulfasalazine treatment, 48 patients (22.3%) received mesalazine treatment, and 55 patients (25.6%) received corticosteroids treatment. Only 19 patients (8.8%) received immunomodulators and 3 patients (1.4%) received infliximab treatment. There was no significant difference between the non-delayed diagnosis group and the delayed diagnosis group regarding medication history.

Types of first CD-related intestinal surgery

There were 90 patients (41.9%) with a history of colectomy (Table 3), 70 patients (32.6%) with a history of ileocecal resection, and 71 patients (33.0%) with a history of ileal resection. Only a small percentage of patients had an enterostomy (8.8% for ileostomy and 3.3% for colostomy).

There were 21 patients (9.8%) who received their first CD-related intestinal surgery as an emergency surgery.

The association between delayed diagnosis and first CD-related intestinal surgery

Patients in the delayed diagnosis group tended to receive more ileal resections as the first CD-related intestinal surgery than the non-delayed diagnosis group (47.8% vs. 26.4%, respectively, $p=0.002$), as shown in Table 3. However, patients in the delayed diagnosis group receive fewer ileocecal resections for the first time than in the non-delayed diagnosis group (22.4% vs. 37.2%, respectively, $p=0.032$). The rates of colectomy, ileostomy, and colostomy were not significantly different between the 2 groups.

The proportion of emergency surgery as the first CD-related intestinal surgery in the delayed diagnosis group was markedly higher than in the non-delayed diagnosis group (4.7% vs. 20.9%, respectively, $p=0.001$).

As Figure 1 shows, the mean interval from the first appearance of CD-related symptoms to the first CD-related intestinal surgery was longer among patients in the delayed diagnosis group ($p<0.05$).

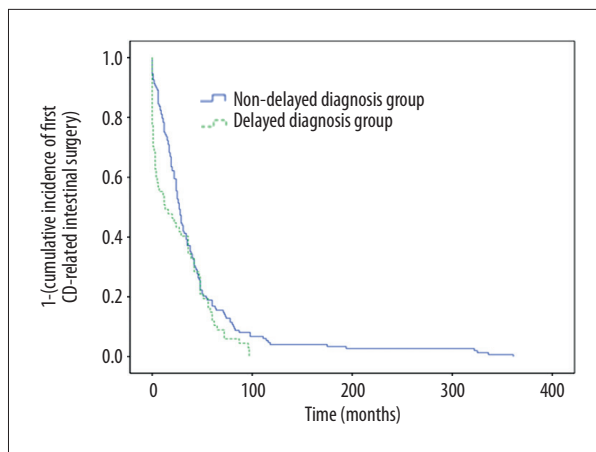


Figure 1. Kaplan-Meier curve of the mean interval time from the first appearance of CD-related symptoms to the first CD-related intestinal surgery.

Discussion

We found that early and emergency need for first Crohn's disease-related intestinal surgery was associated with delayed diagnosis in a Chinese CD cohort from a single center. These results were consistent with findings in a French cohort [11], suggesting that delayed diagnosis is associated with an early need for intestinal surgery.

Based on a previous study from our department [10], delayed diagnosis was defined as a diagnostic interval of more than 34 months, which was much longer than that reported in other cohort studies: Swiss [13] 24 months, French [6] 13 months, Italian [7] 18 months, Romanian [8] 18 months, and Korean [9] 18 months. There appears to be a gap between China and other countries, especially developed countries, regarding CD care within the healthcare system.

In our study, the time from the first appearance of the CD-related symptoms to the first intestinal surgery in the delayed diagnosis group was obviously shorter. Therefore, an early need for the first CD-related intestinal surgery was associated with delayed diagnosis. This suggests that the diagnostic interval should be shortened to the greatest extent possible, thus reducing the risks of CD-related intestinal surgery, and delaying the first intestinal surgery as long as possible.

In our study, patients in the delayed diagnosis group tended to receive the first CD-related intestinal surgery as an emergency surgery. In general, patients with a longer diagnostic interval have a longer course of disease, which generally indicates more severe disease [14]. These patients may need emergency surgery when CD-related symptoms develop.

The age at diagnosis in the delayed diagnosis group was significantly older than in the non-delayed diagnosis group. This was consistent with the results of our previous study [15], showing that age >40 years at diagnosis is one of the risk factors for delayed diagnosis.

There was no significant difference between the non-delayed diagnosis group and the delayed diagnosis group regarding medication history. However, in our department, most CD patients receive sulfasalazine, mesalazine, and corticosteroids as the main medical treatment. This is different from the medications and therapeutic approaches reported in some studies from Western countries, which prefer thiopurines and monoclonal antibodies. In China [15,16], monoclonal antibodies (like infliximab and adalimumab) are too expensive to prescribe for patients. Immunomodulators [17], such as thiopurines, may cause severe complications (e.g., myelosuppression and severe liver function damage), which need to be closely monitored. Immunosuppressants are not widely used in China; their use would also cause financial hardship to many patients. In view of costs, we prefer sulfasalazine and mesalazine.

In the present study, 62.9% of CD patients had at least 1 intestinal operation, which was significantly higher than in other similar studies. Our center is a surgical department, and the majority of patients visited our department with surgical complications (e.g., stenosis, obstruction, and fistula), so it is not surprising to find a relatively higher proportion of patients with an operation history in the study cohort [16].

Compared to the study by Nahon et al., patients in our cohort had a higher rate of ileal resection (33.0% vs. 12.0%) and colectomy (41.9% vs. 15.4%), and lower rate of ileocecal resection (32.6% vs. 66.8%). This was consistent with the characteristics of the lesion distributions in Chinese cohorts [15].

In the present study, patients in the delayed diagnosis group tended to receive ileal resection rather than ileocecal resection during their first operation. The ileum is the most common location of lesions in CD [18], while ileum lesions are difficult to find [19]. Colonoscopy is one of the most common CD diagnostic methods [19–21], and CT-correlated colonoscopy will increase the sensitivity [22]; however, it does not find ileum lesions. Hence, ileum lesions are generally found at the later disease stage. This may be why delayed diagnosis is related to more ileal resections.

This is not the first time that we have looked at delayed diagnosis of CD. In our previous study, we focused on the risks of abdominal surgery and not the impact of the timing of surgery or postoperative prognosis. The present study looked at the relationship between surgical opportunity and delayed diagnosis. Shortening the diagnostic interval and avoiding

delayed diagnosis are crucial to improving the quality of life for CD patients.

There were some limitations to our study that should be considered. The potential risks of selection bias and recall bias should be taken into account, as this was a retrospective study, the sample size was small, and all the participants were recruited from a single center.

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Conclusions

Delayed diagnosis was associated with an early and emergency need for the first CD-related intestinal surgery. The most common type of surgery was ileal resection, and ileocecal resection was uncommon. Delayed diagnosis of CD could be used as a predictive factor of early and emergency need for intestinal surgery. A shorter timeframe for delayed diagnosis could be a new target for the prevention of early surgical treatment in CD patients.

Conflicts of interest

None.