Ulcerative Colitis Overall Disease Severity Index Predicts Colectomy: A Prospective Cohort Study

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Ulcerative colitis overall disease severity index predicts colectomy: a prospective cohort study

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ABSTRACT

Background: ulcerative colitis (UC) overall disease severity index (DSI) has been established. A prospective cohort study was performed to find the value of DSI to predict colectomy within one and four years and explored the association between DSI and other indexes.

Methods: the hospitalized UC patients were enrolled from March 2018 to January 2019 in this single center study. DSI, Truelove and Witts criteria, Mayo index and Seo index were assessed by medical records. Outcome was whether to undergo colectomy within one and
four years and was obtained by telephone survey or medical records. Index values of predicting colectomy within one and four years were evaluated using receiver operating characteristics (ROC) curves.

Results: one hundred and thirty-eight of 233 hospitalized UC patients were enrolled. Within one year, the follow-up period was less than one year for six patients and two patients had died. A further nine patients underwent colectomy. The Spearman correlation coefficient between DSI and Truelove and Witts criteria, Mayo index and Seo index were 0.730, 0.839 and 0.843, respectively. Using these indices to predict colectomy within one and four years, the area under the curve of DSI was more than those of other indices and the cut-off value of DSI was 79.

Conclusions: a good correlation of DSI with other indexes was demonstrated. DSI can be used to predict the need for colectomy within one or four years.

Keywords: Overall disease severity index. Ulcerative colitis. Colectomy.

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease that usually begins in young adulthood and lasts throughout life (1). The incidence and prevalence of UC are highest in westernized nations. However, in developing nations, the incidence has increased (2). The incidence of UC in China is among one of the highest in Asia (3,4). Doctors used disease activity to guide the management of UC (5). Truelove and Witts’s criteria include objective factors, and the Mayo index includes clinical and endoscopic subscore, which are two popular indices (6,7). Meanwhile, it is essential to identify the patients who are likely to require colectomy, and to decide when to start rescue medical therapy (8). Although there is a standard surgery, namely ileal pouch-anal anastomosis, post-operative complications are common (9). Factors affecting colectomy rate include disease extent, need for corticosteroids, hospitalization and so forth (10-16). There are some indexes used to predict colectomy, such as the Seo index, but these indexes do not include the factors of disease course (11,14,17).

Indices were developed to evaluate disease activity at a given time. As UC is a progressive disorder, evaluating long-term disease severity (such as colectomy) is needed to guide therapeutic decisions. There were differences between disease activity and disease severity
Disease activity is a single point in time and is established by the inflammatory effect of UC on patient-reported symptoms, presence of biomarkers and endoscopy. However, it disregards the cumulative bowel damage. Disease severity includes activity and history. Fourteen members of the International Organization for the Study of Inflammatory Bowel Diseases have determined the most important features of disease severity for UC until 2016 (18). The concept of disease severity encompasses three main domains: the impact of disease on the patient, inflammatory burden and disease course. Using a conjoint trade-off method, the specialists ranked the features of disease severity to create an overall disease severity index (DSI) of UC (20). The DSI includes 13 attributes: mucosal lesions, daily activity impact, C-reactive protein (CRP) level, biologics use, recent hospitalization, steroid use, anemia, frequency of loose stools, albumin level, disease extent, nocturnal bowel movements, anorectal symptoms and rectal bleeding.

The relationship between DSI and activity indices is still unclear. The value of DSI is also unclear. This study aimed to describe the relationship between DSI and activity indices, and evaluate the ability of DSI to predict the need for colectomy within one and four years.

**MATERIALS AND METHODS**

**Study setting**

This was a prospective cohort study. From March 2018 to January 2019, the hospitalized patients with UC diagnosed with clinical manifestations, endoscopy and histopathological examination were enrolled at the Peking University First Hospital (21). Exclusion criteria: medical records which were not sufficient to finish calculating indexes, treatment with antituberculosis drugs, previous history of colon surgery, pregnancy and lactation.

**Variables and outcomes**

Demographic and clinical information were obtained from electronic record system. The clinical information included all factors of Truelove and Witts activity criteria, Mayo index, Seo index and Overall Disease Severity index (6,7,20,22).

The outcome was if patients underwent colectomy within one- and four-year, which was obtained by electronic record system or telephone survey. Follow-up information included disease status (colectomy or death). The flow diagram as seen in figure 1.
Statistical analysis
The normal distribution of data was expressed as the mean ± standard deviation. Non-normal distribution data was expressed as the median (minimum and maximum). Correlations were assessed using the Spearman’s correlation coefficient. The predictive accuracies were determined by the area under the ROC curve. The cut-off value was calculated by obtaining the best Youden index. All analyses were performed using SPSS for Windows version 22.0. A p value less than 0.01 was considered as significant.

RESULTS
Patient details
Among 233 hospitalized UC patients, the study enrolled 138. The proportion of non-native patients was 50.7%. Most patients had moderate to severe activity (Table 1). Six patients had a follow-up period of less than one year. Two patients died. Nine patients underwent colectomy within one year. Over a four-year follow-up period, 13 patients were not followed up and 12 patients underwent colectomy within four years. The reasons for surgery were the failure of medical therapy, toxic megacolon, massive bleeding and perforation.

Correlation analysis
The correlation between DSI and Truelove and Witts criteria, Mayo index and Seo index was high (Spearman 0.730, 0.839 and 0.84, respectively). DSI includes factors of disease course (recent hospitalization, biologics use and steroid use). For the purpose of description, the disease course index was defined as the sum of these three factors. DSI without disease course was defined as DSI minus disease course index. The scatter plot demonstrated that there was no correlation between disease course index and DSI without disease course (Fig. 2). Spearman correlation coefficient between them was 0.426 (p < 0.01). The correlation between DSI without disease course and Truelove and Witts index, Mayo index and Seo index was higher than DSI.

Prediction of colectomy within one year
Of 138 patients, six patients were lost to follow-up and two patients died and thus were excluded. Of 130 patients, nine patients underwent colectomy within one year. The DSI area under curve (AUC) was higher than the Seo index, Truelove and Witts index and Mayo index (Fig. 3A and Table 2A).

The cut-off value of DSI was 79, which was calculated by obtaining the best Youden index. Sensitivity, specificity, positive predictive value and negative predictive value were 88.9%, 78.5%, 23.5% and 99.0%. The importance of the disease course associated factors was assessed. To our surprise, the disease course index AUC was very high (Fig. 3C and Table 2B).

**Prediction of colectomy within four years**

Thirteen patients were lost to follow-up, and two patients died and were excluded from a total of 138 patients within four years. Twelve patients underwent colectomy from a total of 123 patients within four years. The DSI area under curve (AUC) was higher than the Seo index, Truelove and Witts index and Mayo index (Fig. 3B and Table 3A).

The cut-off value of DSI was 79, which was calculated by obtaining the best Youden index. Sensitivity, specificity, positive predictive value and negative predictive value were 75%, 78.4%, 27.3% and 96.7%, respectively. We also assessed the importance of the disease course associated factors, and the disease course index AUC was also very high (Fig. 3D and Table 3B).

**Overall severity index classification within one year**

The cut-off value of DSI was 79, based on which, 130 patients were divided into low-risk or high-risk groups. There were 34 patients in the high-risk group and 96 patients in the low-risk group. Compared with Truelove and Witts activity, there were 40 low-risk patients in the Truelove and Witts activity severe group (40/73); none of these 40 patients underwent colectomy within one year. There were 34 low-risk patients in the Truelove and Witts moderate group (34/35); none of them underwent colectomy within one year. A Mayo score of 6-12 points (including an endoscopic subscore of 2 or more points for UC) indicated moderate-severe activity. The number of patients with moderate-severe activity was 89, including 34 high-risk patients and 55 low-risk patients. Eight of 34 high-risk patients
underwent colectomy within one year and none of the low-risk patients underwent colectomy within one year.

**Overall severity index classification within four years**
The cut-off value of DSI was 79, based on which, 123 patients were divided into low-risk or high-risk groups. There were 33 patients in the high-risk group and 90 patients in the low-risk group. Compared with Truelove and Witts activity, there were 38 low-risk patients in the Truelove and Witts activity severe group (38/70); none of these 38 patients underwent colectomy within four years. Compared with the Mayo index, the number of patients with moderate-severe activity was 84, including 33 high-risk patients and 51 low-risk patients. Nine of 33 high-risk patients underwent colectomy within four years and none of the low-risk patients underwent colectomy within four years.

**DISCUSSION**
DSI is strongly associated with activity indices, but it is better than activity indices to predict colectomy within one or four years. The factors of disease course are very important to increase the ability to predict colectomy within one or four years. In groups of moderate activity (Truelove and Witts) and moderate-to-severe activity (Mayo index), DSI can help doctors to recognize patients likely to undergo colectomy within one or four years. The colectomy rate within one year is 6.92 % (9/130), which is higher than another study (4.4 %) (23). The reasons may be: a) inflammatory bowel disease (IBD) patients were included from a teaching hospital; b) 50.7 % of patients were transferred from outside the hospital; and c) 71 % of patients had extensive colitis (14,15).

As DSI encompasses the impact of disease on patient and inflammatory burden, DSI shares some similar characteristics with activity indices. Truelove and Witts criteria includes bloody stools per day, pulse, temperature, hemoglobin and erythrocyte sedimentation rate (ESR). Similarly, DSI includes stool frequency per day, anemia and C-reactive protein (CRP). Mayo index includes rectal bleeding, frequency of bowel motions, mucosa and the physician’s global assessment. Consistently, DSI also includes rectal bleeding, frequency of loose stools, mucosal lesions and daily activity impact. Seo index includes bloody stool, bowel movements, ESR, hemoglobin and albumin. Consistently, DSI also includes rectal bleeding,
frequency of loose stools, CRP, hemoglobin and albumin. That is why DSI has a good correlation with these indices.

The difference between DSI and activity indices was that DIS also encompasses disease course. Disease course reflects the history of the disease, which is not associated with disease activity. The disease course is highly associated with the risk of colectomy. History of medical hospitalization, the use of corticosteroids and the absence of clinical response after induction with infliximab (IFX) are disease course factors which predict the need for colectomy (15,16,24). Thus, DSI is better than activity indices to predict colectomy within one or four years. The positive predictive value of DSI to predict colectomy within one year is 23.5%. There are some other risk factors associated with colectomy which are not included in DSI, such as colonic dilatation, the requirement for blood transfusion, malnutrition and total parenteral nutrition (11,14). We surprisingly found that DSI can better predict the need for colectomy within one year than within four years, which indicated that the ability to predict the risk of surgery in the near future might be more reliable than in the long term. The timely identification of high-risk patients through DSI may be very meaningful.

In clinical practice, physicians use the Truelove and Witts’ criteria for severe disease assessment and management (5). DSI can help physicians to recognize the high-risk patients with moderate activity, who may need intensive care. Biologics are recommended for the treatment of moderate-to-severe UC, which was defined as a Mayo score of 6-12 points (including an endoscopic score of 2 or more points for UC) (25). In moderate-to-severe patients, high-risk patients can be recognized by DSI, but whether receiving intensive care can change their outcome is still unknown. Although immunomodulators and biological therapy are more widely used than before, the colectomy rate does not decrease (26).

The study is limited by the fact that data were collected from a single hospital. Additional larger studies of DSI will validate the cut-off value of predicting the outcome.

**CONCLUSIONS**

In conclusion, the present study demonstrates that DSI has a good correlation with activity indices. Thus, it is better than activity indices to predict the need for colectomy within one or four years. The disease course is important for the value of prediction. DSI can recognize
patients with high-risk colectomy with moderate activity of Truelove and Witts’ criteria and moderate-to-severe activity of the Mayo index, and physicians should pay more attention to these patients. Future studies will validate the cut-off value of DSI.

REFERENCES
20. Siegel CA, Whitman CB, Spiegel BMR, et al. Development of an index to define overall disease severity in IBD. Gut 2018;67(2):244-54. DOI: 10.1136/gutjnl-2016-312648


Table 1. Characteristics of 138 study patients

<table>
<thead>
<tr>
<th>Items</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of males</td>
<td>70 (50.7 %)</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>44.2 ± 15.5</td>
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<tr>
<td>Non-native</td>
<td>70 (50.7 %)</td>
</tr>
<tr>
<td>Median duration of disease (year)</td>
<td>3 (0-30)</td>
</tr>
<tr>
<td>Newly diagnosed patient</td>
<td>27 (19.6 %)</td>
</tr>
<tr>
<td>Location of disease</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>6 (4.3 %)</td>
</tr>
<tr>
<td>Left-sides</td>
<td>34 (24.6 %)</td>
</tr>
<tr>
<td>Extensive</td>
<td>98 (71.0 %)</td>
</tr>
<tr>
<td>5-aminosalicylic acid</td>
<td>135 (97.8 %)</td>
</tr>
<tr>
<td>Medication exposure</td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>51 (37.0 %)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>8 (5.8 %)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9 (6.5 %)</td>
</tr>
<tr>
<td>Truelove and Witts activity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25 (18.1 %)</td>
</tr>
<tr>
<td>Moderate</td>
<td>81 (58.7 %)</td>
</tr>
</tbody>
</table>
32

Severe

(23.2 %)

)

Accepted Article
Table 2. ROC curve information within one year

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>p value</th>
<th>95% confidence interval</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI</td>
<td>0.781</td>
<td>0.005</td>
<td></td>
<td>0.631</td>
<td>0.930</td>
</tr>
<tr>
<td>Seo index</td>
<td>0.692</td>
<td>0.055</td>
<td></td>
<td>0.536</td>
<td>0.849</td>
</tr>
<tr>
<td>Mayo index</td>
<td>0.758</td>
<td>0.01</td>
<td></td>
<td>0.580</td>
<td>0.935</td>
</tr>
<tr>
<td>Truelove and Witts index</td>
<td>0.660</td>
<td>0.111</td>
<td></td>
<td>0.487</td>
<td>0.833</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>p value</th>
<th>95% confidence interval</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI</td>
<td>0.781</td>
<td>0.005</td>
<td></td>
<td>0.631</td>
<td>0.930</td>
</tr>
<tr>
<td>DSI without disease course</td>
<td>0.675</td>
<td>0.081</td>
<td></td>
<td>0.505</td>
<td>0.845</td>
</tr>
<tr>
<td>Disease course index</td>
<td>0.852</td>
<td>0.000</td>
<td></td>
<td>0.770</td>
<td>0.934</td>
</tr>
</tbody>
</table>

DSI: disease severity index; AUC: area under curve.
Table 3. ROC curve information within four years

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>p value</th>
<th>95% confidence interval</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI</td>
<td>0.680</td>
<td>0.041</td>
<td>0.505</td>
<td>0.854</td>
<td></td>
</tr>
<tr>
<td>Seo index</td>
<td>0.597</td>
<td>0.466</td>
<td>0.380</td>
<td>0.748</td>
<td></td>
</tr>
<tr>
<td>Mayo index</td>
<td>0.644</td>
<td>0.102</td>
<td>0.450</td>
<td>0.838</td>
<td></td>
</tr>
<tr>
<td>Truelove and Witts index</td>
<td>0.564</td>
<td>0.466</td>
<td>0.381</td>
<td>0.784</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index</th>
<th>AUC</th>
<th>p value</th>
<th>95% confidence interval</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI</td>
<td>0.680</td>
<td>0.041</td>
<td>0.505</td>
<td>0.854</td>
<td></td>
</tr>
<tr>
<td>DSI without disease course</td>
<td>0.582</td>
<td>0.351</td>
<td>0.405</td>
<td>0.759</td>
<td></td>
</tr>
<tr>
<td>Disease course index</td>
<td>0.813</td>
<td>0.000</td>
<td>0.722</td>
<td>0.904</td>
<td></td>
</tr>
</tbody>
</table>

DSI: disease severity index; AUC: area under curve.
233 eligible patients

138 patients

28 via medical records

108 via telephone survey

102 finish telephone survey

6 lost to follow-up
  - number not exist
  - not answer for 3 times

130 follow-up more than 1 year

123 follow-up more than 5 years

95 excluded
  - Medical records were not complete for indexes
  - treatment with antituberculosis drugs
  - previous history of colon surgery
  - pregnancy
  - lactation

Fig. 1. Flow diagram.
Fig. 2. Scatter plot of disease course index and overall disease severity index (DSI) without disease course. The scatter plot demonstrated that there was no correlation between disease course index and DSI without disease course.
Fig. 3. A. ROC curves for overall disease severity (DSI), Seo index, Mayo index and Truelove and Witts index for the prediction of colectomy within one year. B. ROC curves for overall disease severity (DSI), disease course index, and DSI without disease course in the prediction of colectomy within four years. C. ROC curves for overall disease severity (DSI), disease course index, and DSI without disease course for the prediction of colectomy within one year. D. ROC curves for overall disease severity (DSI), disease course index, and DSI without disease course for the prediction of colectomy within four years.