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Increased modified DUBLIN scores are associated with serious ulcerative colitis and treatment failure

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Abstract

Background: Grading of endoscopic lesions is important for determining the severity of ulcerative colitis and developing treatment strategies, but the commonly used methods are not sufficient.

Objectives: This study aimed to investigate whether new endoscopic scoring systems incorporating lesions and disease extent are associated with clinical disease severity and maintainable remission.

Design: This was a retrospective study. In all, 110 patients with ulcerative colitis were included and 87 completed 12-month follow-up.

Methods: Colonoscopy was performed within 1 week before blood samples were taken. Degree of ulcerative colitis burden of luminal inflammation (DUBLIN) scores were calculated as the product of Mayo endoscopic score (MES) by disease extent and ulcerative colitis endoscopic index of severity was used to replace MES when calculating modified DUBLIN scores.

Results: DUBLIN and modified DUBLIN scores were increased in the moderate and severe groups significantly ($p < 0.05$). Both of increased scores contributed to the detection of serious diseases, and the clinical cutoff values of DUBLIN and modified DUBLIN were 3[area under the curve (AUC) = 0.809, $p = 0.001$) and 7(AUC = 0.815, $p = 0.001$), respectively. They were with high sensitivity, but the specificity of DUBLIN was lower. Both scores were correlated to partial Mayo scores, C-reactive protein and erythrocyte sedimentation rate positively, and they were correlated to the albumin negatively ($p < 0.05$). Higher modified DUBLIN scores (>7) were associated with an increased risk of treatment failure (hazard ratio = 4.96, 95% confidence interval: 1.17–21.00, $p = 0.03$), but there were no association between DUBLIN scores and long-term remission ($p > 0.05$).

Conclusion: Increased DUBLIN and modified DUBLIN scores were conducive to screening serious disease, but only modified DUBLIN scores had the potential to assist in making an upgraded therapeutic schedule.

Keywords: endoscopic assessment, inflammatory burden, maintainable remission, ulcerative colitis

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Introduction

Ulcerative colitis (UC) is a recurrent colorectal disease, which is becoming more and more prevalent in developed and newly industrialized countries. UC leads to the decline of patient's physical function and participation in social work.[1] Determining the inflammation burden of UC is conducive to making therapeutic plans, thus saving social sources.

Physicians often use symptom-based scores [partial Mayo score (PMS)), biochemical indicators,

and endoscopic information to determine disease severity. The clinical assessment is subjective and lack of stability.[2] CRP and ESR are commonly used serum biomarkers and correlated to the endoscopic activity modestly.[2,3] But the sensitivity of CRP is lower, and ESR is with opposite characteristics.[3] Fecal calprotectin (FC) has good sensitivity for predicting sustained clinical response, but its predictive value for complete remission is unclear.[2,4] Mucosal healing has become the main target of clinical treatment,[2] but the methods commonly used to evaluate endoscopic lesions are insufficient.[5]

The Mayo endoscopic score (MES) and ulcerative colitis endoscopic index of severity (UCEIS) are most studied by physicians.[2,5] MES is simple and practicable, but it cannot distinguish deep ulcer from superficial.[5] UCEIS includes the assessment of vascular morphology, mucosal bleeding, erosion, and ulceration. It can assess the endoscopic severity more comprehensively.[6] It has been validated in several studies and is superior to MES in predicting the biological agent response and long-term outcomes of UC patients.[5,6,7,8,9] High UCEIS is associated with increased risk of colectomy.[9] But both scoring systems focus only on the mucosal lesions, none of them include the extent. Extensive colitis is more likely to develop colorectal cancer, and undergo surgery in future.[10,11] These results indicate that the disease extent should be included in the consideration for luminal inflammation burden. The degree of ulcerative colitis burden of luminal inflammation (DUBLIN) score is calculated as a product of MES and disease extent, which is correlated to serum biomarkers and associated with clinical outcomes, such as treatment failure and readmission.[12,13] However, most studies were conducted in single center.[12,13,14] Due to the narrow range of MES (0–3), the distribution of DUBLIN scores is not wide. It should be further validated before widely used in clinical practice. Because UCEIS has more scores (0–8) than MES, we hypothesized that using UCEIS in the modified DUBLIN scoring system may be more beneficial to assess patients' inflammation burden.

Thus, the aims of this study are (1) to assess whether new scoring systems were useful to detect serious disease and (2) to evaluate the utility of new scores in predicting long-term clinical outcomes.

Methods

Subjects

Consecutive patients of UC who were first hospitalized in our department from 2016 to 2021 were enrolled in the retrospective study. Patients were excluded if they had the following conditions: unable to undergo colonoscopy due to severe intestinal obstruction; gastrointestinal tumors; previous abdominal surgery; women in the pregnancy or breast-feeding stage; and severe connective tissue disease; severe renal, cardiac or pulmonary disease. Ultimately, 110 patients were included. Colonoscopy was performed within 1 week before blood samples were taken. The treating physicians were blinded to the endoscopic scores and made the treatment independently.

Finally, 87 patients completed 12-month follow-up. The clinical symptoms were recorded monthly intervals for 12 months after treatment. They was recorded as PMSs including stool frequency, hematochezia, and the global assessment by physician.[12] Clinical remission was defined as without use of corticosteroids and PMS $\leqslant 2$ with no sub-score > 1.[12] Treatment failure was defined as introduction/escalation of biologic agents, introduction of immunosuppressant (azathioprine was permitted in patients taking steroids as induction therapy), and use of steroids or surgery during follow-up.[12]

The study protocol and the recruitment of the patients were approved by the Ethics Committee of Zhongshan Hospital Xiamen University (Ethical approval No: xmzsyyky 2022-240). Written informed consent was obtained from all individuals before starting any study procedure. We confirmed that all methods were performed in accordance with the relevant guidelines and regulations. We have de-identified all patient details. The reporting of this study conforms to the STROBE statement.[15] The checklist from the relevant guideline was submitted as supplementary material

Standards of grading for disease severity

Mayo scores were used to assess clinical disease severity at diagnosis. The total score $\leqslant 2$ without sub-score >1 suggested remission, 3–5 with mild activity, 6–10 with moderate, and 11–12 with severe.[16]

The colonoscopy procedures were performed by the same physician (Chenxi Xie). A complete colonoscopy should include the whole colon and enter 20 cm into the end of ileum. The withdrawal time should be more than 6 min. The MES and UCEIS were used to evaluate the most severely inflamed part under endoscopy. MES is from 0 to 3: Score 0 was without active disease; score 1 for erythema, decrease vascular pattern, and mild friability; score 2 for erythema, absent vascular pattern, and friability, and score 3 for ulcer and bleeding.[5,17] Three endoscopic variables were recorded to calculate UCEIS: vascular pattern (0 = normal, 1 = patchy obliteration, 2 = obliterated); bleeding (0 = none, 1 = mucosal, 2 = luminal mild, 3 = luminal moderate or severe); erosion and ulcer (0 = none, 1 = erosions, 2 = superficial ulcer, 3 = deep ulcer). UCEIS is the sum of these scores.[5,6]

The disease extent was defined as follows[12]: E1 = proctitis/proctosigmoiditis; E2 = left-sided colitis; E3 = pancolitis. The DUBLIN scores were calculated as the product of MES by extent and were from 0 to 9. The modified DUBLIN scores were calculated as the product of UCEIS by extent and were from 0 to 24.

Assessment of serum indicators

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and albumin were assessed as the serum inflammatory indicators in the study. Two milliliters of blood samples were taken after fasting for at least 8 h. All assays were performed according to the instructions of specialized Roche instruments by an investigator blinded to the patients' status.

Statistical analysis

Data are expressed as either the mean ± standard deviation or the median (interquartile range). One-way analysis of variance (ANOVA) was used to compare differences if the values for a metric followed normal distribution; otherwise, the rank-sum test was used. The cutoff values of endoscopic scoring systems were obtained by receiver operator characteristic curve (ROC) to distinguish serious disease from mild. Kaplan–Meier curves were used to describe the change of maintainable remission rate in patients with different endoscopic scores. The Spearman rank correlation coefficient was used to analyze the correlation between endoscopic scores and PMS or the levels of serum biomarkers. Cox regression was used to analyze the correlation between endoscopic scores and the possibility of maintaining long-term remission. A p value less than 0.05 was considered statistically significant. The statistical analysis was accomplished using SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics of the patients

A total of 127 UC patients who were first hospitalized in our department from 2016 to 2021 were screened. Five with a history of intestinal surgery and 12 unable to tolerate endoscopy were excluded from this study. Ultimately, 110 patients were included and 87 completed the 12-month follow-up (Table 1).

E1 was more prevalent in mild group, and E3 was more prevalent in patients with serious disease ($p < 0.05$). The levels of CRP, ESR increased and ALB decreased significantly in the severe group when compared to that of mild group ($p < 0.05$), but the differences were not significant between patients with mild and moderate disease ($p > 0.05$).

In terms of initial therapy, 87 patients were taking mesalazine, 9 with immunosuppressant, 36 with corticoid, 19 with biological agents, and 2 underwent surgery. Among the patients, 22 were treated with mesalazine and corticoid, 5 were treated with corticoid and immunosuppressant, and 9 were taking biological agents combined with corticoid.

Application of endoscopic scoring systems to distinguish patients with serious disease

The scores of MES, UCEIS, DUBLIN, and modified DUBLIN were increased significantly in the moderate and severe groups when compared to that of mild (all $p < 0.05$), but the differences were not significant between the two groups (all $p > 0.05$) (Table 2).Therefore, we divided the patients into two groups: with mild and with moderate/severe disease.

The cutoff value of MES to distinguish moderate/severe from mild group was 2.5[area under the curve (AUC) = 0.855, $p = 0.00$), the sensitivity

Table 1. Demographic data of the patients at diagnosis.

	Mild ($n=11$)	Moderate ($n=67$)	Severe ($n=32$)	p Value
Age (years)	51.09 ± 13.98	42 ± 13.76	46.50 ± 13.31	0.07
Male (%)	81.82%	68.66%	53.13%	0.153
BMI (kg/m^2)	21.76 (20.83, 24.73)	21.57 (19.45, 23.64)	21.82 (18.08, 23.55)	0.678
Disease extent				0.029
E1	6	13	3	
E2	1	7	3	
E3	4	47	26	
Disease duration (years)	3 (2, 13)	2 (0.2, 5)	3 (0.25, 6)	0.162
CRP (mg/L)	2.29 (0.67, 8.17)	7.79 (2.08, 27.76)	39.03 (9.16, 101.46)	0.000
ESR (mm/h)	11.20 (6.18, 28.38)	22.80 (11.40, 36.40)	27.20 (23.70, 48.58)	0.000
ALB (g/L)	40.65 (38.80, 42.37)	38.00 (34.09, 41.70)	32.20 (27.76, 36.50)	0.010

One-way ANOVA was used to compare the differences of age in patients with different disease severity. Kruskal–Wallis H test was used to compare the differences of BMI, disease duration, CRP, ESR, and ALB among three groups. Disease extent was ordered variable and rank-sum test was used. Chi square test was used to compare the difference in gender distribution among three groups.
BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2. Comparison of the endoscopic scores among patients classified by Mayo scores.

	Mild ($n=11$)	Moderate ($n=67$)	Severe ($n=32$)	p Value
MES	2 (2, 2)	3 (3, 3)[a]	3 (3, 3)[a]	0.00
UCEIS	3 (2, 4)	5 (4, 6)[a]	5 (5, 6)[a]	0.00
DUBLIN	2 (2, 6)	9 (6, 9)[a]	9 (9, 9)[a]	0.00
Modified DUBLIN	4 (3, 6)	12 (8, 18)[a]	15 (12.75, 18)[a]	0.00

Kruskal–Wallis H test was used to compare the differences of different endoscopic scoring systems among three groups. $p<0.05$ means that the distribution of values in each group is not equal. The letter a means that the difference is significant when compared to the mild group separately.
DUBLIN, degree of ulcerative colitis burden of luminal inflammation; MES, Mayo endoscopic score; UCEIS, ulcerative colitis endoscopic index of severity.

was 86.9%, and the specificity was 81.8%. Since the nearest value on the coordinate point of ROC was 1.5, the score of 2 was chosen as the clinically useful cutoff point.

The cutoff value of UCEIS to distinguish moderate/severe from mild group was 4.5(AUC = 0.818, $p=0.001$), the sensitivity was 65.7%, and the specificity was 90.9%. The nearest values on the coordinate point of ROC were 3.5 and 5.5, but the latter with same specificity as 4.5. Therefore, the score of 5 was chosen as the clinically useful cutoff point.

The cutoff value of DUBLIN to distinguish moderate/severe from mild group was 2.5(AUC = 0.809, $p=0.001$), the sensitivity was 96%, and the specificity was 54.5%. Since the

nearest values on the coordinate point of ROC were 3.5, the score of 3 was chosen as the clinically useful cutoff point.

The cutoff value of modified DUBLIN to distinguish moderate/severe from mild group was 7 (AUC = 0.815, $p = 0.001$), the sensitivity was 80.8%, and the specificity was 81.8%.

It seemed that the new endoscopic scoring systems were useful to find patients with serious disease, especially the modified DUBLIN scores. DUBLIN and modified DUBLIN scores were correlated to PMS positively (both $p < 0.05$). They were correlated to CRP and ESR positively, and correlated to the albumin negatively (all $p < 0.05$) (Figure 1).

Application of new endoscopic scores in the evaluation of long-term remission

In all, 87 patients finished the 52 week follow-up and 61 still maintained remission without escalation of therapy. Two patients who initially underwent surgery were not included in the follow-up. Of the 87 patients, mesalazine was used in 46, corticoid was used in 25, and biological agents were used in 16 patients to induce remission. Eight patients were taking biological agents combined with corticoid. Eight patients were unable to obtain remission from the initial treatment, so the time to treatment failure was recorded as 'zero'. The comparison of metrics between two groups was shown in Table 3.

The Kaplan–Meier curves were used to describe the time to treatment failure in patients dividing by the clinical cutoff values of endoscopic scores (Figure 2).

There was no significant difference between patients with high and low MES (for log rank, $p = 0.819$, for Breslow, $p = 0.748$). The result was similar in the groups divided by DUBLIN scores (for log rank, $p = 0.063$, for Breslow, $p = 0.067$).

More patients maintained remission in the group with lower UCEIS (for log rank, $p = 0.003$, for Breslow, $p = 0.002$). The hazard ratio (HR) for treatment failure in high UCEIS group was 2.98 [95% confidence interval (CI): 1.36–6.48] ($p = 0.006$).The mean time of maintaining remission was 48.58 (95% CI: 45.14–52.01) weeks in low UCEIS group, and was 37.42 (95% CI: 28.95–45.89) weeks in high UCEIS group.

More patients maintained remission in the group with lower modified DUBLIN scores (for log rank, $p = 0.013$, for Breslow, $p = 0.015$). The HR for treatment failure in the group with higher scores was 4.96 (95% CI: 1.17–21.00) ($p = 0.03$). The mean time of maintaining remission in the group with lower scores was 50.87 (95% CI: 46.19–55.55) weeks, and in the other group was 42.34 (95% CI: 37.52–47.16) weeks.

Discussion

Mucosal inflammation under endoscopy is correlated to the symptoms in UC. Complete clinical remission without diarrhea and blood in stool is well associated with endoscopic healing (EH).[2] In fact, symptomatic remission and normalized serum biomarkers are short or intermediate therapeutic targets, but to achieve EH and normalization of life quality should be higher goals.[2] This indicates the importance of endoscopic scoring in the diagnosis and follow-up of UC patients.

A simple and validated endoscopic index is needed for the evaluation of disease activity. MES and UCEIS are simple and convenient for physicians. EH can be considered as MES = 0 or UCEIS $\leqslant$ 1 point.[2] However, both scores are without segmental assessment. This may be a deficiency to reflect the whole luminal inflammatory burden. UC colonoscopic index of severity and modified MES include disease extent in the scoring formula.[18,19] But the complex calculation may limit their clinical application. Therefore, we manage to evaluate the potential utility of new endoscopic scoring systems in the management of UC.

In this study, all the endoscopic scores were increased significantly in patients with moderate or severe disease. This was consistent with previous report.[13] The AUC of four endoscopic scores to distinguish serious UC was similar. We found that MES and modified DUBLIN scores were with excellent sensitivity and specificity. It seemed that the specificity of UCEIS was highest, but its sensitivity was obvious lower than the others. DUBLIN was with opposite characteristics. This may limit the use of DUBLIN as an alternative to MES for endoscopic screening. Both new scoring systems were correlated to the PMS that based on

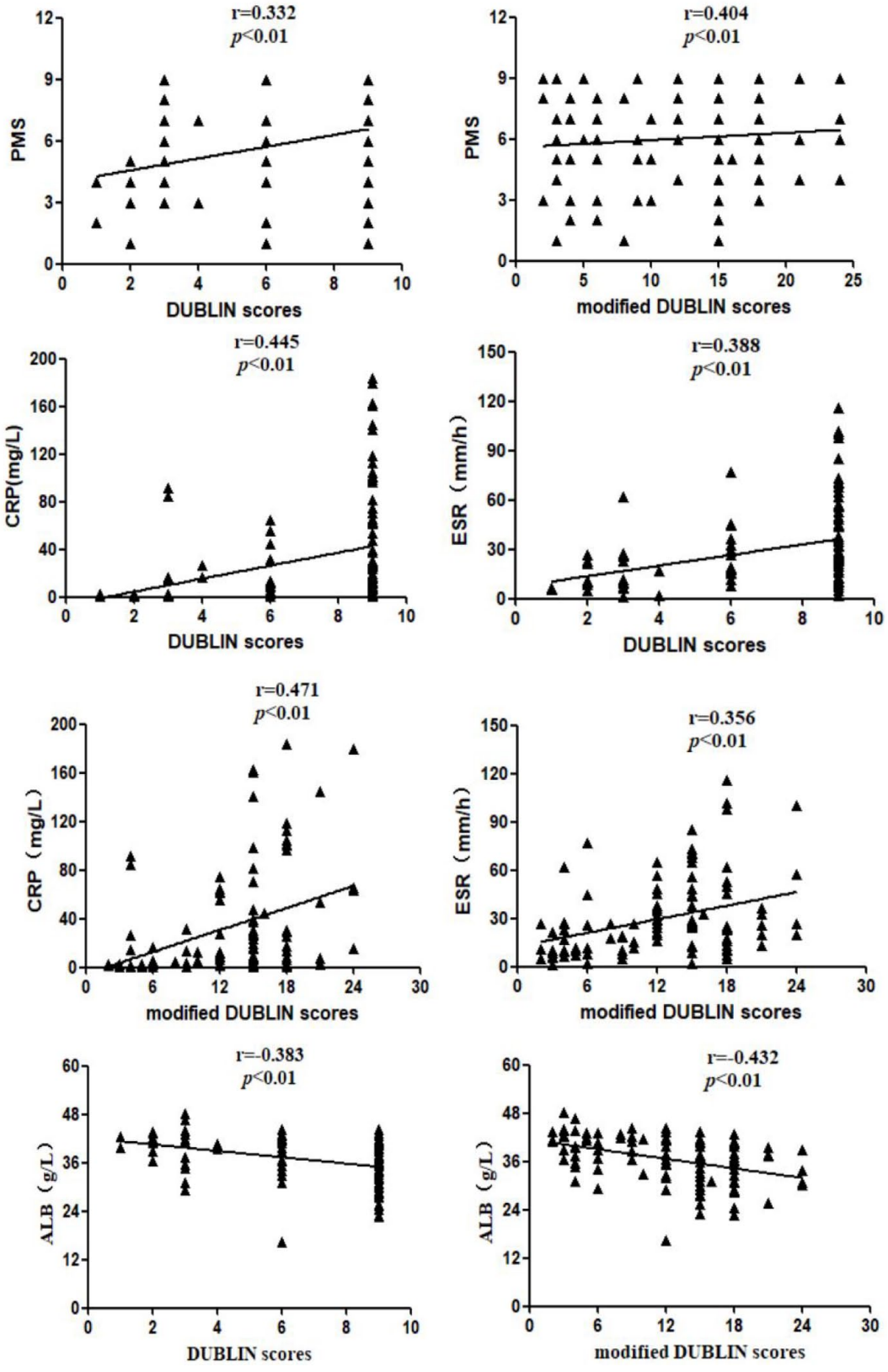

Figure 1. Correlation between DUBLIN, modified DUBLIN scores and PMS, serum inflammatory indicators.
DUBLIN, degree of ulcerative colitis burden of luminal inflammation; PMS, partial Mayo score.

Table 3. Comparison of metrics between patients with and without maintaining remission.

	Remission ($n = 61$)	Relapse ($n = 26$)	p Value
Age (years)	44 ± 12.95	45.69 ± 15.83	0.603
Male (n)	43	19	0.807
BMI (kg/m^2)	21.68 (19.58, 23.55)	21.57 (18.18, 22.67)	0.333
Disease duration (years)	2 (0.50, 5)	2 (0.28, 5)	0.893
Disease extent			0.034
E1	16	2	
E2	7	2	
E3	38	22	
MES	3 (3, 3)	3 (3, 3)	0.777
UCEIS	5 (3.50, 6)	6 (4, 6)	0.012
Use of biological agents (n)	8	8	0.100
Use of corticoid (n)	20	13	0.130
CRP (mg/L)	5.32 (1.74, 33.98)	16.30 (8.55, 64.41)	0.007
ESR (mm/h)	19.80 (10.20, 30.45)	26.60 (19.50, 40.80)	0.029
ALB (g/L)	37.60 (35.39, 41.85)	34.33 (30.93, 39.55)	0.039

Age followed normal distribution, and one-way ANOVA was used to compare the difference between two groups. Disease duration, BMI, MES, UCEIS, CRP, ESR, and ALB were continuity variables, and Wilcoxon rank-sum test was used. Disease extent was ordered variable and rank-sum test was used. The differences in gender distribution, using biological agents or corticoid as initial therapy were compared by chi square test.
ANOVA, analysis of variance; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MES, Mayo endoscopic score; UCEIS, ulcerative colitis endoscopic index of severity.

subjective symptoms. These results supported that lesion extent should be taken into account when evaluating the disease severity, and the modified DUBLIN would be a useful index in clinical practice.

ESR and CRP are most widely used indicators in UC, and they were correlated to the endoscopic activity moderately.[2] Therefore, it was not surprising to find that both UCEIS scores and the levels of two indicators were lower in patients with long-term remission. Because DUBLIN and modified DUBLIN scores incorporated both mucosal inflammation and the extent of involvement, it was not surprise to find positive correlation between them and the two serum biomarkers. This result supported the probability of reflecting luminal inflammation burden by the two scoring systems. In the study, we found ALB was lower in patients with poor prognosis. Decreased serum albumin was suggested to be a predictor of poor response for biological agents.[20,21] This may due to the common protection mechanism from catabolism for both albumin and monoclonal antibodies.[22] The new endoscopic scores were correlated to the albumin negatively, which indicated a potential association between higher new scores and poor therapy response.

There were not significant differences in the age, gender, weight, and disease duration between patients with or without long-term remission. In fact, the impact of these factors on maintenance therapy is controversial, and our results were consistent with some previous studies.[22,23,24] Both corticoid and biological agents are effective to induce remission, but the maintenance is affected by complicating factors. Therefore, it was

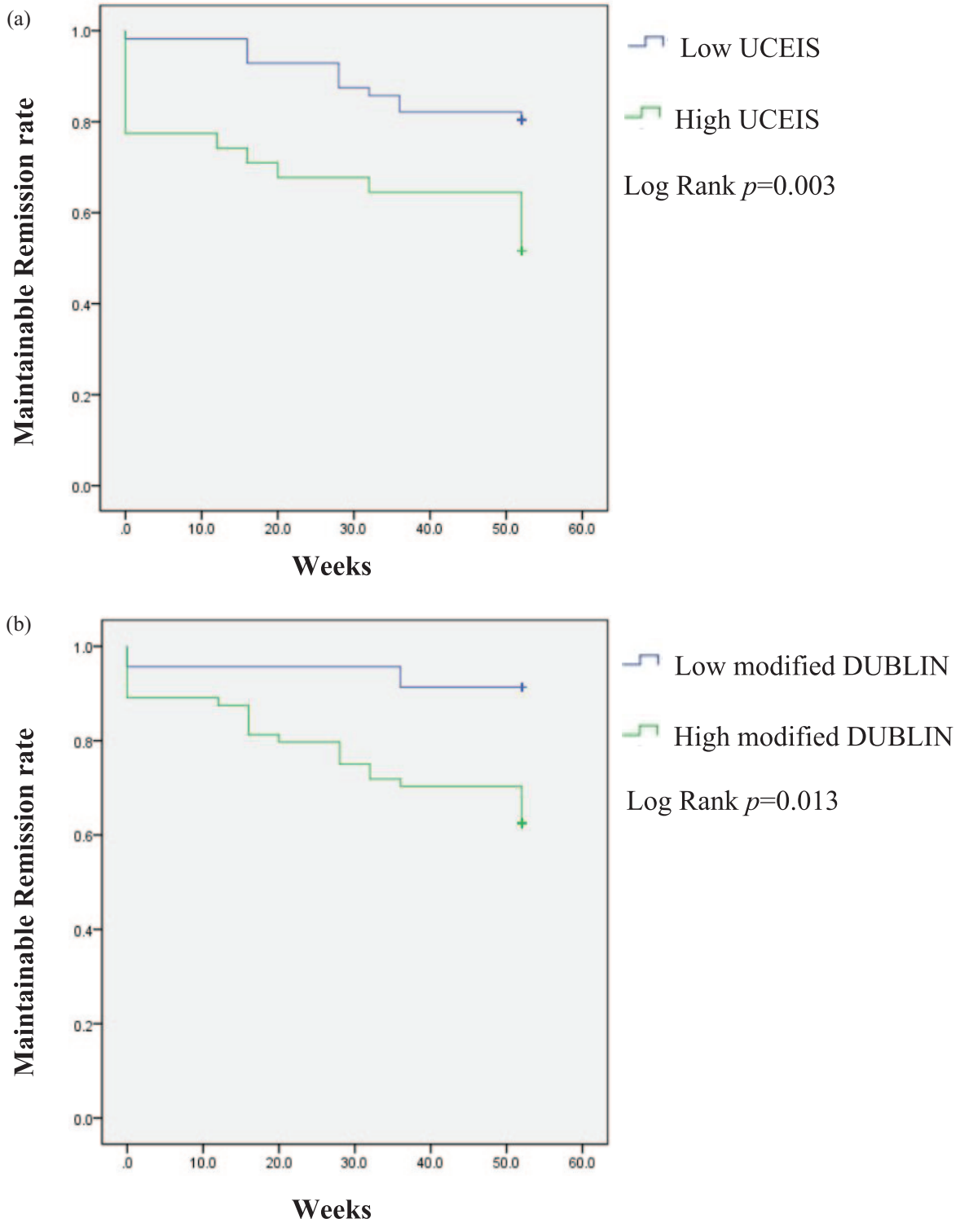

Figure 2. The difference of time to treatment failure in patients with high and low UCEIS or modified DUBLIN scores. (a) High UCEIS > 5 (b) High modified DUBLIN score > 7.
DUBLIN, degree of ulcerative colitis burden of luminal inflammation; UCEIS, ulcerative colitis endoscopic index of severity

reasonable that no significant difference in drug use could be found between two groups.

More pancolitis could be found in the group without maintainable remission. The location is not a reliable marker to predict therapy response, although poorer response may be found in extensive disease.[22,25] The values of MES were similar between two groups. This may be due to the narrow scoring range of MES. More detailed evaluation on endoscopic lesions was necessary. UCEIS had notable advantage when compared with MES, and we found its scores was significant lower in patients with maintenance of therapy response. These results suggested that incorporated UCEIS and disease extent may be useful to the prediction of poor prognosis. Then we studied the influence of new scoring systems on maintainable remission and found that the prognosis was similar in patients with different degree of MES and DUBLIN score. This was consistent with the results of univariate analysis. The groups with lower UCEIS and modified DUBLIN scores may maintain remission for a long time, and patients with increased modified DUBLIN scores may have higher risk of relapse than those with increased UCEIS alone.

Many scores have been developed to estimate the risk of requiring second-line therapy or colectomy for acute severe UC, but there are certain limitations.[12,26] A new scoring system named Toronto inflammatory bowel disease (IBD) global endoscopic reporting score has been introduced lately, which took into account all visualized colorectal segments.[27,28] This was beneficial to evaluate endoscopic full disease burden for IBD patients, but further studies were needed to validate the new scoring system, especially on the contribution of stenosis to the index.[28] It seemed that the modified DUBLIN score was practical for physicians due to the easy calculation and the association with disease severity and prognosis, but it was not appropriate to make therapeutic decision relying on a single score alone. We admitted that comprehensive consideration was needed when the physicians made treatment schedule.

There are some limitations in this study. First, this was a single-center retrospective study and our data only from hospitalized patients and their follow-up. Multicentre studies including outpatients were needed to confirm the conclusion. Second, not all patients completed endoscopic evaluation during follow-up. Prospective assessment would be useful to further validate the association of modified DUBLIN score with inflammation burden. Third, due to the relatively small size of patients completed follow-up, we did not conduct subgroup analysis. Therefore, the reliability of our conclusion should be further verified. We will focus on the predictive value of modified DUBLN system for treatment failure in patients treated with corticoid or biological agents in future study. Fourth, FC has been proved to outperform CRP and ESR in predicting endoscopic activity and clinical relapse in UC,[2,29,30] but this biomarker was not included in our study. This was due to the lack of making quantitative detection in our hospital. Studies on the correlation between FC levels and modified DUBLIN scores would be helpful to determine the role of new scoring system in making personalize therapy.

Conclusion

DUBLIN and modified DUBLIN scores were associated with the severity of UC. The sensitivity and specificity of modified DUBLIN score were high in distinguishing moderate/severe UC from the mild, but the lower specificity of DUBLIN score may limit its clinical application. Increased UCEIS and modified DUBLIN scores were useful to screen the potential patients who may loss response during follow-up. In summary, our study suggested that measuring modified DUBLIN scores would help physicians develop targeted treatment programs effectively.

Declarations

Ethics approval and consent to participate

The study protocol and the recruitment of patients were approved by the Ethics Committee of Zhongshan Hospital Xiamen University (Ethical approval No: xmzsyyky 2022-240). Written informed consent was obtained from all individuals before starting any study procedure.

Consent for publication

Not applicable.

Author contribution(s)

Lupeng Liu: Conceptualization; Data curation; Formal analysis; Investigation.

Hui Ouyang: Data curation; Formal analysis; Investigation.

Jingling Su: Data curation; Formal analysis.

Yumei Lin: Data curation; Formal analysis; Investigation.

Yiqun Hu: Formal analysis; Methodology; Project administration.

Huaxiu Shi: Methodology; Project administration.

Chenxi Xie: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
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Supplemental material
Supplemental material for this article is available online.

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