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Original Article

ORIGINAL ARTICLE

Development and validation of a nomogram to predict indolent course in patients with ulcerative colitis: a single-center retrospective study

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Abstract

Background: The natural disease course for patients with ulcerative colitis (UC) is heterogeneous and few data are available on the indolent course of UC and its related factors. We aimed to develop and validate a nomogram to predict indolent course in patients with UC.

Methods: Data of patients diagnosed with UC in the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between April 2007 and February 2021 were retrospectively analysed. Indolent course was defined as a disease course without need for strict interventions (steroids, immunomodulators, biological agents, hospitalization, or surgery therapy) during the follow-up period. The whole cohort was randomly divided into training set and validation set. The nomogram was constructed in the training set based on the results of univariate and multivariate Cox regression analyses. The performance of the nomogram was assessed by the concordance index (C-index), area under the receiver-operating characteristic curve (AUC), and calibration plots. In addition, we internally validated the nomogram via the bootstrap method and the validation set.

Results: Of 969 treatment-naive patients with UC, 771 (79.6%) had an indolent course after diagnosis. Of these, 313 patients were included in the development and validation of the nomogram. The nomogram incorporating age, disease activity, C-reactive protein, and platelet count showed good calibration and discrimination. The C-index was 0.759 (0.741 in bootstrap validation) and the AUC at 2, 4, and 6 years was 0.767, 0.782, and 0.775, respectively. The nomogram performed well when applied to the validation set.

Conclusion: A majority of patients with UC had an indolent course after diagnosis. The nomogram developed in this study might be useful in therapeutic decision-making and follow-up management for patients with UC.

Key words: ulcerative colitis; indolent course; predict; nomogram

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Introduction

Ulcerative colitis (UC), a subtype of inflammatory bowel disease (IBD), is a chronic relapsing and progressive disorder with unclear etiology [1]. Current therapeutic drugs for UC include 5-aminosalicylic acid (5-ASA) drugs, steroids, immunomodulators, and biological agents, and promising therapeutic drugs targeting specific signaling pathways involved in the pathogenesis of IBD have continued to be investigated in recent years [2, 3]. Among these, 5-ASA is the fundamental therapy for patients with UC, especially for mild to moderate UC [4, 5]. With the frequent relapse and the progression of disease, drug escalation and even surgical therapy are further needed. Notably, the natural disease course of UC is heterogeneous among patients. As reported in a systematic review, a majority of patients with UC are most active at diagnosis, and in remission or mild activity in the subsequent disease course; ~10%–15% patients have an aggressive course [6]. For some patients, 5-ASA therapy is sufficient for clinical remission induction and maintenance during the relatively long-term course after diagnosis, while others require strict interventions at diagnosis or need treatment escalation within a shorter time. Accordingly, reliable prediction for the disease course of patients with UC is of great significance to guide therapeutic decision-making and follow-up management, but it is still a challenge.

In previous studies, intensification therapy in medicine and the requirement for surgery were generally considered as signs of complicated or aggressive disease course in patients with UC [7–9]. To provide more effective therapy approaches for these patients at the appropriate time, researchers have conducted multiple studies to find disease-course-associated predictors at diagnosis [7–9]. However, few data are available on the indolent course of UC and its related factors. Recently, Yanai *et al.* [10] defined indolent course in Crohn's disease as a disease course without the need for strict interventions (including steroids, immunomodulators, biological agents, hospitalization, or surgery therapy) during the whole follow-up period. As noted above, we believe that the definition of indolent course in Crohn's disease may also apply to patients with UC.

In this study, we aimed to uncover factors associated with the indolent course of patients with UC and to develop and validate a nomogram for prediction.

Patients and methods

Study population

Patients diagnosed with UC at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between April 2007 and February 2021 were included in the study. Inclusion criteria were as follows: (i) had a definite diagnosis of UC; (ii) age $\geq$16 years; (iii) treatment-naive (no history of steroids, immunomodulators, biological agents, or surgery therapy for UC); and (iv) initiate treatment with 5-ASA or sulfasalazine after diagnosis. Exclusion criteria included the following: (i) pregnancy; (ii) accompanied by other immune diseases; (iii) follow-up duration <3 months; or (iv) lack of research data. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (No. [2022] 128).

Data collection

Demographic and clinical characteristics of patients with UC at diagnosis were collected, including gender, age, disease duration (time from symptoms to diagnosis in our center), smoking history (never vs current/past smoking), body mass index, disease location (according to the Montreal classification) [11], extra-intestinal manifestation, endoscopic score (according to the Mayo endoscopic score) [12], and disease activity (according to the modified Mayo score) [12]. Disease location and endoscopic score were assessed via reviewing endoscopic images captured at the time of diagnosis. Laboratory data at enrollment including C-reactive protein (CRP), erythrocyte sedimentation rate, white blood cells, red blood cells, hemoglobin, platelet (PLT), alanine aminotransferase, aspartate aminotransferase, albumin, and urea were also extracted.

Definition and end point

Indolent course was defined as a disease course without the need for strict interventions (steroids, immunomodulators, biological agents, hospitalization, or surgery therapy) throughout the entire follow-up. The primary end point of this study was the first strict intervention after enrollment.

Development of nomogram

Univariate Cox regression analysis was used to find the potentially relevant variables of the indolent course and the factors with a *P*-value <0.1 were further included in the multivariate analysis. Variables in the final model were selected by the backward stepwise method. Hazard ratio (HR) together with 95% confidence interval (CI) were calculated. A nomogram was further developed based on the variables in the final model.

Assessment and validation of nomogram

Patients with UC were randomly divided into training set and validation set in a 7:3 ratio based on the experience of similar studies in other diseases [13–15]. The concordance index (C-index) and calibration plots were obtained to assess the discrimination and calibration of the nomogram, respectively. Area under the time-dependent receiver-operating characteristic curve (AUC) was calculated to evaluate the predictive accuracy of the nomogram at different time points. The nomogram was internally validated by the bootstrap method with 1,000 resamples and the validation set.

Statistical analysis

Quantitative variables are presented as median and interquartile range (IQR) and qualitative variables are presented as frequencies and percentages. Comparisons between the training set and validation set were conducted using Wilcoxon rank-sum tests and Chi-squared tests or Fisher's exact tests. The optimal cut-off values of the quantitative variables were obtained at the maximum of Youden index (sensitivity + specificity − 1) from the receiver-operating characteristic curve analysis. If the number of patients in two groups differed a lot when grouped based on the optimal cut-off values, we used median as cut-off values instead. An indolent disease time curve of UC was generated using the Kaplan–Meier method. The randomization of patients with UC was performed using the 'caTools' package. Nomogram, the C-index, and calibration plots were obtained using the 'rms' package. Time-dependent receiver-operating characteristic curves were plotted using the 'riskRegression' package. All statistical analyses were two-sided and performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, USA) and R software, version 4.1.1 (R Foundation for Statistical Computing). $P < 0.05$ was considered as statistically significant.

Results

Demographic and clinical characteristics of patients

We reviewed the medical records of 1,242 patients with UC who were treated at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between April 2007 and February 2021. Of 969 patients who were treatment-naive, 771 (79.6%) had an indolent course after establishing a definite diagnosis of UC. In the subsequent analysis of factors associated with an indolent course of UC, 458 cases were further excluded. Finally, 313 patients with UC were included and were randomly divided into training set ($n = 219$) and validation set ($n = 94$) (Figure 1). The demographic and clinical characteristics of patients are shown in Table 1. The two sets were comparable except for urea (4.5 [IQR, 3.6–4.9] mmol/L vs 4.2 [IQR, 3.5–4.7] mmol/L; $P = 0.021$). In the training set and validation set, the median age at enrollment was 39.0 (IQR, 30.0–49.0) and 41.5 (IQR, 31.0–52.0) years, respectively; both sets were mainly composed of patients with mildly and moderately active disease; the median CRP was 1.11 (0.78–2.93) and 1.08 (0.78–3.82) mg/L, respectively; the median follow-up time was 33.6 (IQR, 13.0–62.6) and 33.7 (IQR, 11.5–63.7) months, respectively.

Cumulative probabilities of maintaining an indolent course in UC patients

In total, 43 of 219 (19.6%) patients in the training set and 19 of 94 (20.2%) patients in the validation set required strict interventions during follow-up, respectively (Table 2). There was no significant difference in the presence of end-point events between the two sets (19.6% vs 20.2%; $P = 0.906$). None of the patients required UC-related surgery in the two sets.

In the training set, 6 patients were hospitalized for UC and 37 patients required steroids (23 of 37), immunomodulators (7 of 37), or biologic therapy (7 of 37). In the validation set, 9 patients were hospitalized for UC and 10 patients needed steroids (8 of 10), immunomodulators (1 of 10), or biologic therapy (1 of 10). For the whole cohort, the cumulative probabilities of maintaining an indolent course were consistently >60% (Figure 2).

Development and assessment of the nomogram

For patients with UC in the training set, the results of univariate and multivariate Cox regression analyses are presented in Table 3. Among 19 variables, 5 (age, disease location, clinical activity, CRP level, and PLT count) were further included in the multivariate analysis. Four variables were retained in the final model as independent predictors for the indolent course of treatment-naive patients with UC: age >43 years (HR, 3.750; 95% CI, 1.990–7.067; $P < 0.001$), moderate to severe disease (HR, 3.202; 95% CI, 1.729–5.931; $P < 0.001$), CRP >1.32 mg/L (HR, 2.656; 95% CI, 1.397–5.049; $P = 0.003$), and PLT count $>240 \times 10^9$/L (HR, 3.401; 95% CI, 1.655–6.988; $P = 0.001$). The above four variables were further used to develop a nomogram (Figure 3A).

In the training set, the prediction model yielded a C-index of 0.759 (95% CI, 0.683–0.835) and the C-index generated by the

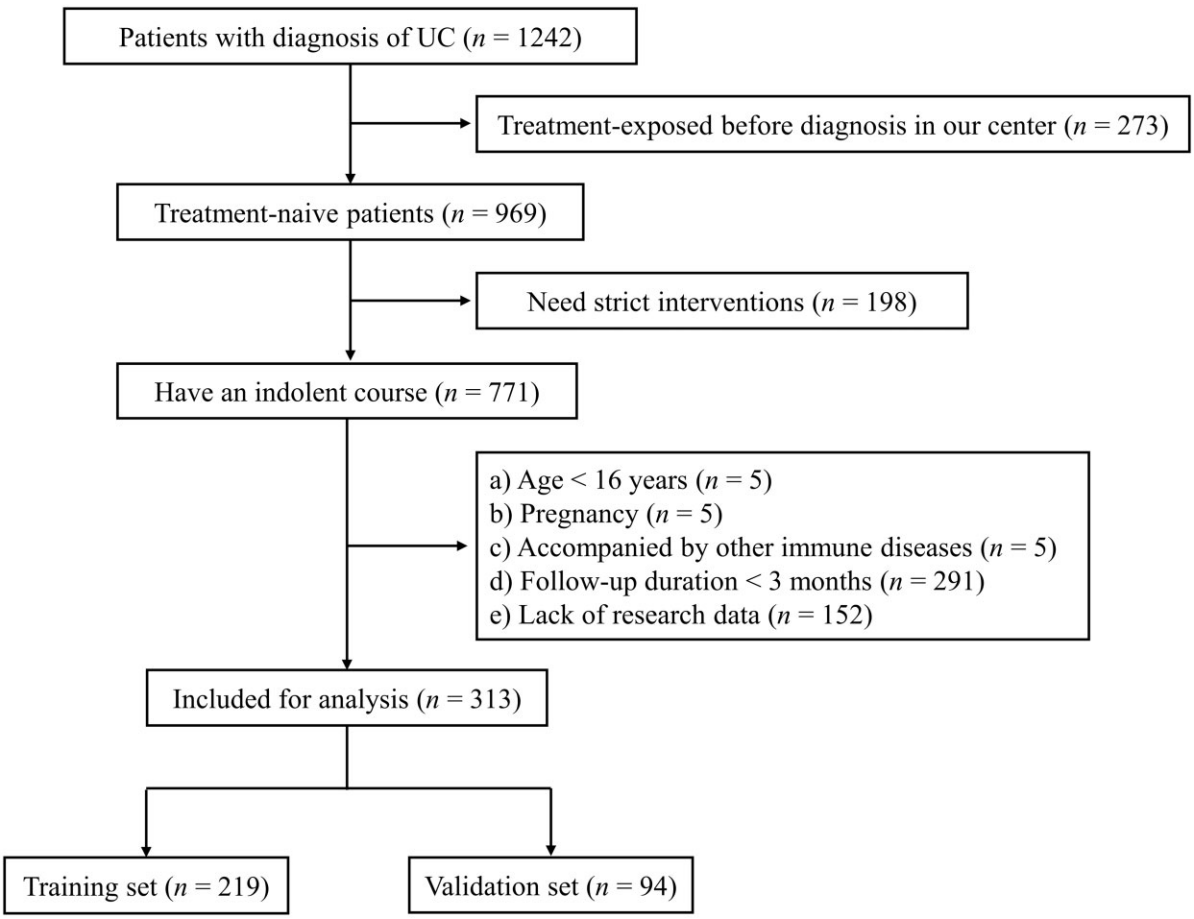

Figure 1. The flow chart of ulcerative colitis patient enrollment

Table 1. Demographic and clinical characteristics of 313 patients with ulcerative colitis

Characteristic	Training set ($n = 219$)	Validation set ($n = 94$)	*P*-value
Male, *n* (%)	143 (65.3)	56 (59.6)	0.335
Age, years, median (IQR)	39.0 (30.0–49.0)	41.5 (31.0–52.0)	0.304
Disease duration, months, median (IQR)	12.0 (5.0–41.0)	12.0 (3.0–24.8)	0.199
History of smoking[a], *n* (%)	23 (11.9)	17 (19.5)	0.088
BMI, kg/m^2, median (IQR)	20.5 (19.3–22.3)	21.4 (19.4–23.1)	0.106
Disease location[b], *n* (%)			0.527
Proctitis (E1)	83 (37.9)	34 (36.2)	
Left-sided colitis (E2)	86 (39.3)	33 (35.1)	
Extensive colitis (E3)	50 (22.8)	27 (28.7)	
Extra-intestinal manifestation, *n* (%)	28 (12.8)	13 (13.8)	0.802
Endoscopic score[c], *n* (%)			0.952
1	35 (16.0)	16 (17.0)	
2	117 (53.4)	48 (51.1)	
3	67 (30.6)	30 (31.9)	
Clinical activity[d], *n* (%)			0.710
Remission	1 (0.5)	4 (4.3)	
Mild	147 (67.1)	56 (59.5)	
Moderate	69 (31.5)	30 (31.9)	
Severe	2 (0.9)	4 (4.3)	
Total follow-up time, months, median (IQR)	33.6 (13.0–62.6)	33.7 (11.5–63.7)	0.732
CRP, mg/L, median (IQR)	1.11 (0.78–2.93)	1.08 (0.78–3.82)	0.702
ESR, mm/h, median (IQR)	16 (8–28)	15 (8–28)	0.744
WBC, $\times 10^9$/L, median (IQR)	6.57 (5.65–7.80)	6.59 (5.35–8.42)	0.866
RBC, $\times 10^{12}$/L, median (IQR)	4.77 (4.38–5.16)	4.70 (4.29–5.03)	0.271
HB, g/L, median (IQR)	138 (127–150)	137 (123–149)	0.551
PLT, $\times 10^9$/L, median (IQR)	254 (210–300)	237 (212–289)	0.704
ALT, U/L, median (IQR)	17 (12–25)	17 (14–24)	0.829
AST, U/L, median (IQR)	21 (17–25)	21 (18–24)	0.890
ALB, g/L, median (IQR)	43.5 (40.8–46.0)	43.9 (40.4–45.9)	0.843
Urea, mmol/L, median (IQR)	4.5 (3.6–4.9)	4.2 (3.5–4.7)	0.021
Presence of end-point events, *n* (%)	43 (19.6)	19 (20.2)	0.906

IQR, interquartile range; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; RBC, red blood cell; HB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin.
[a]Data were applicable for only 281 of the 313 patients.
[b]According to the Montreal classification.
[c]According to the Mayo endoscopic score.
[d]According to the modified Mayo score.

Table 2. End-point events in patients with ulcerative colitis

Event	Training set ($n = 43$)	Validation set ($n = 19$)
Hospitalization	6 (14.0)	9 (47.4)
Surgery	0 (0.0)	0 (0.0)
Requirement of medications	37 (86.0)	10 (52.6)
Steroids	23	8
Azathioprine	5	1
Thalidomide	1	0
Methotrexate	1	0
Infliximab	5	1
Vedolizumab	2	0

internal bootstrap validation was 0.741. The AUC at 2, 4, and 6 years was 0.767 (95% CI, 0.674–0.861), 0.782 (95% CI, 0.695–0.868), and 0.775 (95% CI, 0.666–0.884), respectively (Figure 3B). As shown in the calibration plots, good calibration was observed for the probability of prediction and observation in the training set (Figure 3C–E).

When applying the nomogram in the validation set, the C-index of the prediction model was 0.654 (95% CI, 0.509–0.799). As presented in Figure 4A, the AUC at 2, 4, and 6 years was 0.711 (95% CI, 0.516–0.907), 0.632 (95% CI, 0.458–0.807), and 0.647 (95% CI, 0.469–0.825), respectively. Regarding the calibration of the model, the predicted probabilities were close to the observed probability, with a slight deviation (Figure 4B–D).

Discussion

The present study demonstrated that a majority (79.6%) of treatment-naive patients with UC had an indolent disease course after diagnosis, which was similar to the results of a previous population-based inception cohort study [16]. In addition, our study indicated that a relatively high proportion of patients with UC could maintain an indolent course over the long follow-up period. Our study is the first to survey the persistence of indolent course over time and investigate the potential predictors of indolent course in patients with UC. Four factors including age >43 years, moderate to severe disease, CRP >1.32 mg/L, and PLT count >240 $\times 10^9$/L were found to be

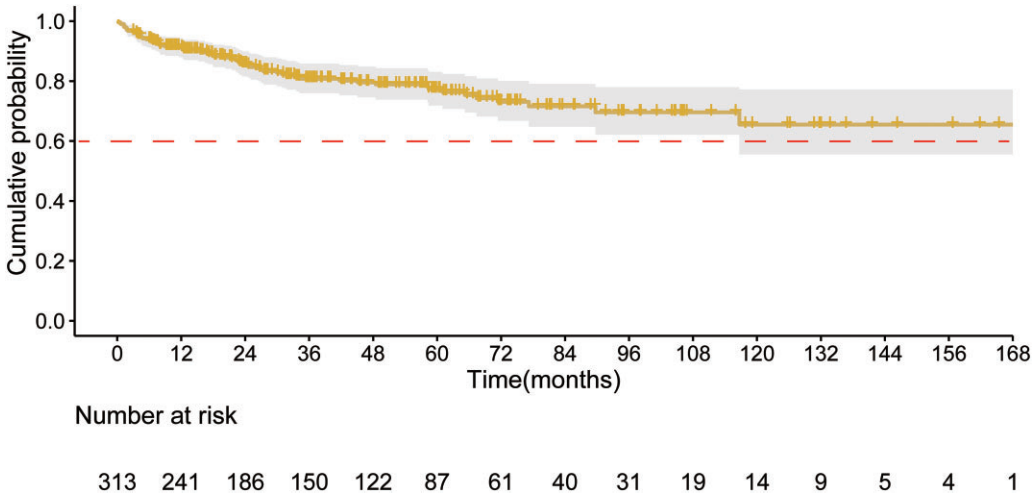

Figure 2. The cumulative probabilities of maintaining an indolent course in patients with ulcerative colitis

Table 3. Univariate and multivariate Cox regression analyses in patients with ulcerative colitis of the training set

Factor	Univariate		Multivariate (backward stepwise)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	1.074 (0.567–2.033)	0.827		
Age >43 years	2.564 (1.401–4.694)	0.002	3.750 (1.990–7.067)	<0.001
Disease duration >12 months	1.042 (0.572–1.896)	0.893		
Smoking history	0.495 (0.152–1.604)	0.241		
BMI >20.5 kg/m^2	0.695 (0.379–1.275)	0.240		
Disease location[a]		0.053		
Proctitis (E1)	Reference			
Left-sided colitis (E2)	1.969 (0.915–4.235)	0.083		
Extensive colitis (E3)	2.712 (1.201–6.124)	0.016		
Extra-intestinal manifestation	1.475 (0.655–3.317)	0.348		
Endoscopic score[b]		0.394		
1	Reference			
2	0.670 (0.293–1.531)	0.342		
3	1.028 (0.440–2.403)	0.949		
Clinical activity[c]				
Remission-mild	Reference		Reference	
Moderate-severe	2.628 (1.442–4.789)	0.002	3.202 (1.729–5.931)	<0.001
CRP >1.32 mg/L	2.283 (1.215–4.289)	0.010	2.656 (1.397–5.049)	0.003
ESR >16 mm/h	1.385 (0.759–2.530)	0.289		
WBC >6.57 × 10^9/L	1.406 (0.769–2.569)	0.269		
RBC >4.77 × 10^{12}/L	0.672 (0.364–1.239)	0.203		
HB >138 g/L	0.772 (0.421–1.415)	0.402		
PLT >240 × 10^9/L	2.878 (1.413–5.863)	0.004	3.401 (1.655–6.988)	0.001
ALT >17 U/L	0.871 (0.478–1.586)	0.651		
AST >21 U/L	1.088 (0.597–1.982)	0.782		
ALB >43.5 g/L	0.733 (0.400–1.342)	0.314		
Urea >4.5 mmol/L	1.023 (0.560–1.869)	0.940		

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; RBC, red blood cell; HB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; HR, hazard ratio; CI, confidence interval.
[a]According to the Montreal classification.
[b]According to the Mayo endoscopic score.
[c]According to the modified Mayo score.

negative predictors for the indolent disease course of patients with UC. Prediction for indolent course at diagnosis might help clinicians in determining who is less likely to need intensive medical therapy during the follow-up, which may help to avoid over-treatment and facilitate personalized follow-up strategies. The nomogram in our study was constructed based on the routine clinical data and laboratory tests, which are easy to be implemented in clinical practice.

Diagnosis age is generally considered to contribute to the prediction of prognosis and disease course in patients with UC. Young age at diagnosis (<40 years) was often found to be a predictor of aggressive disease course such as increased risk of

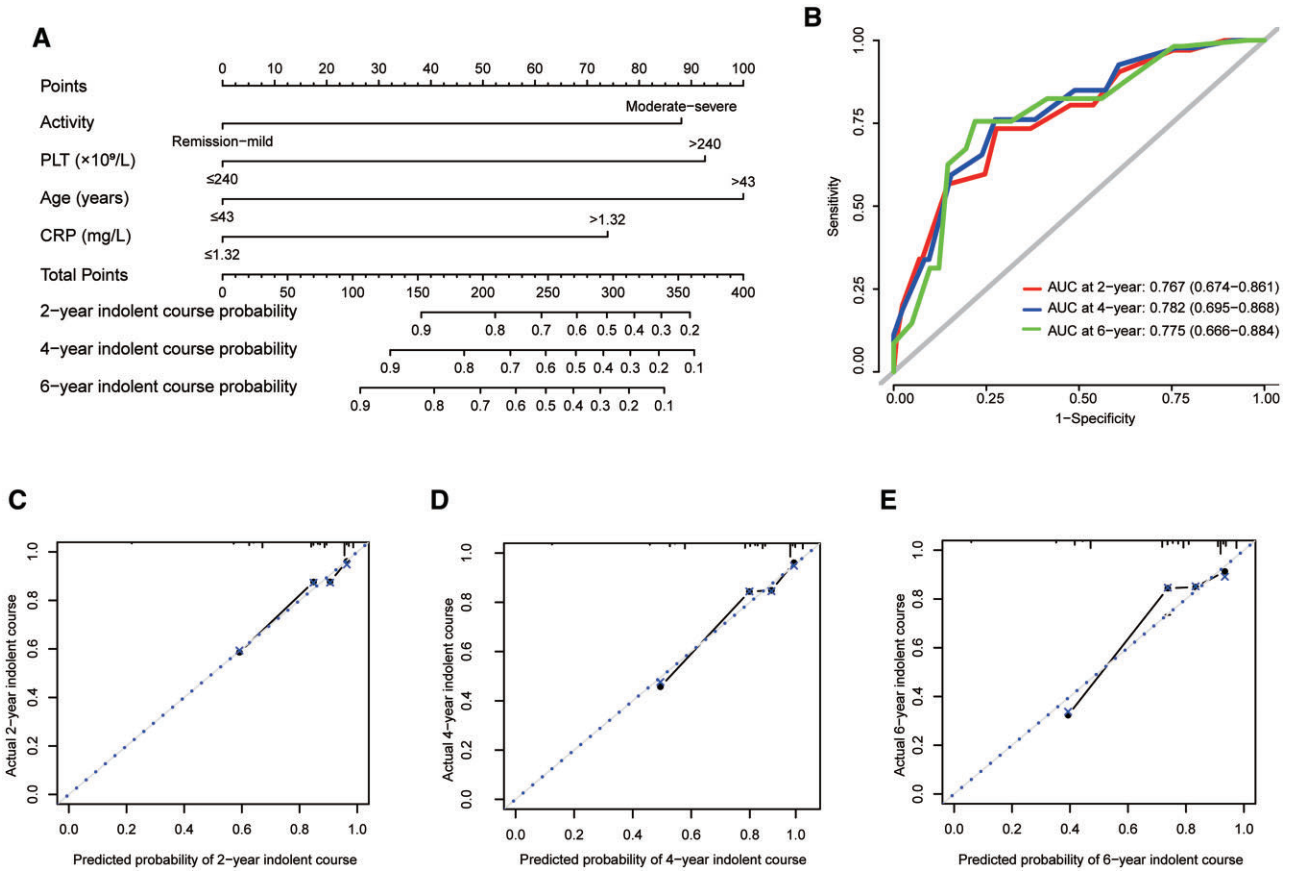

Figure 3. The display and evaluation of the model for prediction of indolent course in the training set. (A) Nomogram. (B) Time-dependent receiver-operating characteristic curve. (C)–(E) Calibration plots at 2, 4, and 6 years, respectively. PLT, platelet count; CRP, C-reactive protein; AUC, area under the time-dependent receiver-operating characteristic curve.

disease relapse or colectomy and anti-TNF exposure after diagnosis [6]. However, age of >43 years was identified as a risk factor for the indolent course of UC patients in our study. Although the definition of the study end point was not completely the same as that in our study, the results of Waterman *et al.* [8] provided support for our conclusions. They divided patients with UC into three groups (mild UC, moderate UC, and severe UC) according to the requirement for hospitalization, medication, and colectomy during follow-up. After the correlation analysis with baseline data, they indicated that age >40 years at diagnosis was associated with severe UC. We speculated that the differences of other clinical baseline characteristics may have contributed to the controversial conclusions. The relationship between age and indolent disease course in patients with UC need to be further investigated and validated in future studies. The presence of moderate or severe disease at diagnosis has also been identified to be a significant predictor for disease relapse and later colectomy of patients with UC in previous studies [17]. Similarly, we found that moderate to severe disease at diagnosis was negatively associated with the indolent course of UC patients.

CRP is a major acute-phase protein produced mainly by hepatocytes under the stimulation of multiple cytokines [18]. In the field of IBD, CRP is commonly used as a serological biomarker for surveillance of disease activity and prediction of clinical response to treatment [19]. Furthermore, a high level of CRP at diagnosis was reported to have predictive power for the risk of hospitalization and colectomy in UC [20]. In the present study, CRP with a cut-off value of 1.32 mg/L provided the maximum accuracy in discriminating between patients with indolent course and those without indolent course during the follow-up period. Patients with CRP >1.32 mg/L were likely to have a shorter indolent course.

Previous studies have observed abnormalities in the number, size, density, and function of PLT in IBD [21]. Researchers proposed that PLT is an inflammatory marker in IBD and the inflammatory potential of PLT may contribute to the pathogenesis of IBD [21]. Our results showed that PLT $>240 \times 10^9$/L was a risk factor for the indolent course of patients with UC. Several studies have demonstrated that an elevated PLT count was a predictor of relapse in UC, which in part supports our finding [22, 23].

We acknowledge that our study has some limitations. First, due to the retrospective nature of this study, some patients had to be excluded for the lack of research data or sufficient follow-up. However, our study had a relatively reliable sample size of patients with UC and met the principle of '10 events per variable' [24]. Admittedly, there is a possible selection bias in the present study, so the results are warranted to be further validated by well-designed studies in the future. Second, although

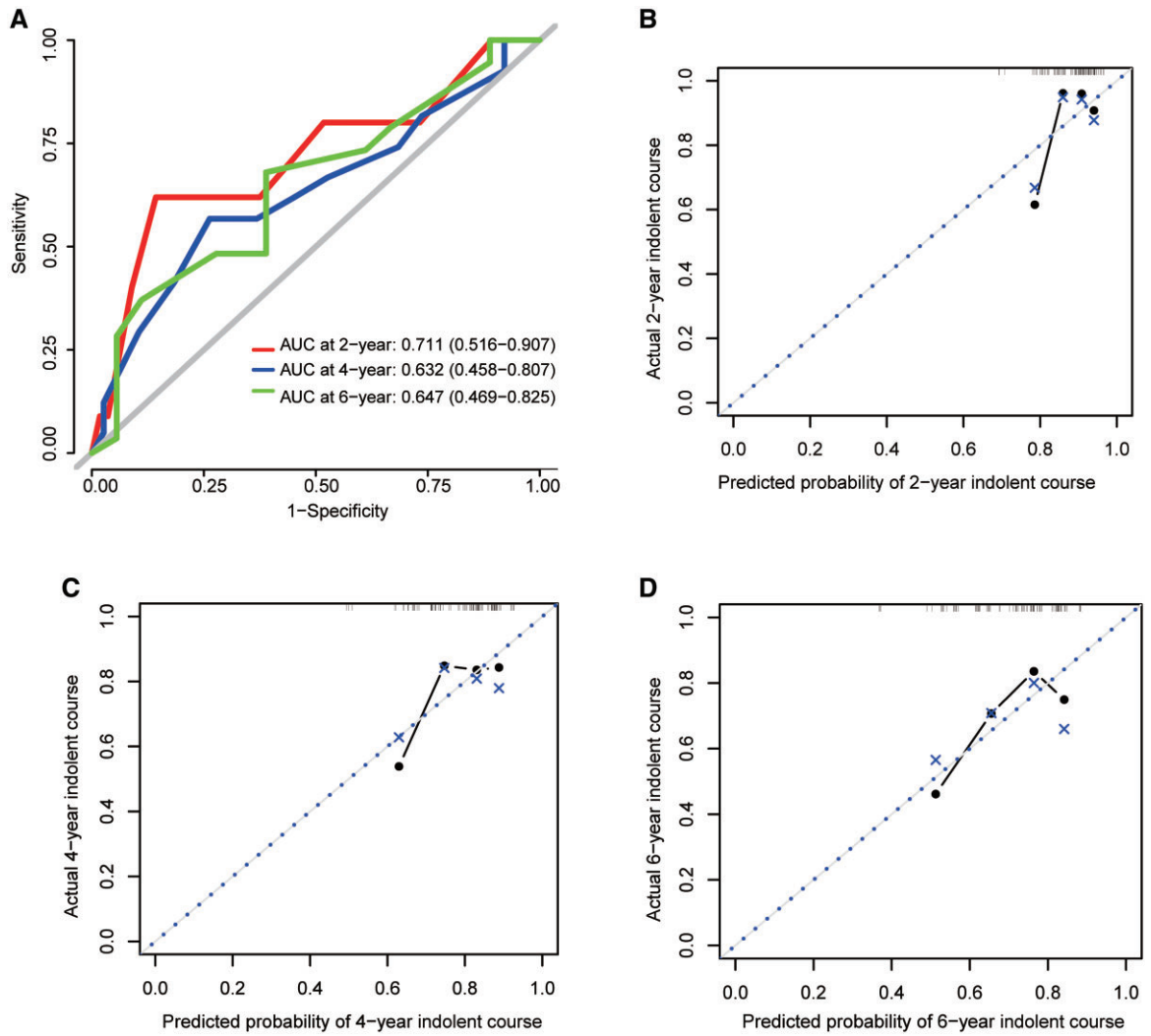

Figure 4. The application of the nomogram in the validation set. (A) Time-dependent receiver-operating characteristic curve. (B)–(D) Calibration plots at 2, 4, and 6 years, respectively. AUC, area under the time-dependent receiver-operating characteristic curve.

we identified factors associated with indolent course in treatment-naive patients with UC and constructed a nomogram, the performance of the prediction model was moderate. Third, the nomogram remains to be externally validated in other centers to confirm its generalizability.

In conclusion, a majority of UC patients had an indolent course after diagnosis and an indolent course in UC could be predicted based on clinical variables at diagnosis. The nomogram incorporating age, disease activity, CRP, and PLT count manifested good performance in predicting the indolent course of UC patients. UC patients who were >43 years old at diagnosis, with moderate to severe disease, CRP >1.32 mg/L, and PLT count $>240 \times 10^9$/L might need more strict follow-up monitoring after diagnosis. This study enriched the knowledge of indolent disease course in patients with UC and had the potential to promote the stratified management and individualized therapy of UC patients. In the future, the findings of this study need to be further validated in other centers and the prediction model of indolent course in UC is worth further development in a prospective study involving a large cohort. In addition, integrating clinical data and the multi-omic data to develop a more accurate and reliable prediction model for indolent course may also be meaningful.

Authors' Contributions

X.Z. and Z.Z. designed the study. N.L., S.Z., and C.L. wrote the manuscript. N.L., T.L., and T.T. collected and analysed the data. B.C., Y.H., and M.C. revised the manuscript. All authors have read and approved the final version of the manuscript.

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None.

Conflict of Interest

None declared.

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