

A Novel Multiparameter Scoring Model for Noninvasive Early Prediction of Ischemic Colitis: A Multicenter, Retrospective, and Real-World Study

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INTRODUCTION: Ischemic colitis (IC) is a common gastrointestinal ischemic disease caused by hypoperfusion or reperfusion injury. However, there are few studies on risk factors associated with poor prognoses of the disease. This study aimed to determine the predictors of poor prognoses in patients with IC and establish a prognostic scoring method with good internal and external validity for identifying severe cases in an early stage.

METHODS: We established a prognosis model by conducting a multicenter, retrospective study of patients hospitalized with IC between November 2008 and May 2020. Predictive power was tested using 5-fold internal cross-validation and external validation.

摘要

目的: 缺血性结肠炎(ischemic colitis, IC)是一种常见的由低灌注或再灌注损伤引起的肠道缺血性疾病。然而,与IC不良预后相关的危险因素的研究极少。本研究旨在确定IC患者预后不良的预测因素,并建立一个经过内、外部数据验证的早期重症患者预后评分模型。

方法: 我们对2008年11月至2020年5月间在两家大型三甲医院确诊为IC的住院患者进行回顾性研究,从而建立预后预测模型并进行验证。模型的预测能力及一致性通过内部五折交叉验证和外部验证来评价。

结果: 预测模型最终纳入了6个与IC不良预后显著相关的预测因子,分别为:中性粒细胞计数、D-二聚体水平、回肠远端缺血、结肠肝曲缺血、肠道溃疡、肠腔狭窄。在模型的验证过程中,内部交叉验证的受试者工作特征曲线下面积(Area Under Curve, AUC)为86%,外部验证的AUC为95%。该模型准确识别了内部队列中88.08%的患者的真实预后情况。另外,我们发现65岁以下的患者的心率越快、中性粒细胞与淋巴细胞比值越高,预后越差。65岁及以上的患者出现回肠末端缺血、结肠肝曲缺血、结肠脾曲缺血及肠腔狭窄时预后较差。

结论: 结肠肝曲或回肠远端局部缺血、内镜下有溃疡或狭窄的证据、中性粒细胞计数或D-二聚体水平较高的患者预后更差。这些信息可以帮助临床医生早期识别预后不良的患者,并给予及时和适当的治疗,以规避不良后果。

Li et al. *Clin Trans Gastroenterol*. 2021
Abstract translated to Mandarin

Clinical and Translational
GASTROENTEROLOGY

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Received October 3, 2020; accepted April 20, 2021; published online June 9, 2021

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RESULTS: The following 6 factors were included in the prognostic model: neutrophil count, D-dimer level, ischemia of the distal ileum, ischemia of the hepatic flexure, ulceration, and luminal stenosis. The area under the receiver-operating characteristic curve for internal cross-validation of the prediction model was 86%, and that for external validation was 95%. During internal validation, our model correctly identified 88.08% of the patients. It was further found that patients younger than 65 years with a higher neutrophil-to-lymphocyte ratio and higher heart rate had poor prognoses. Patients aged 65 years and older with ischemia of terminal ileum, hepatic flexure, splenic flexure, and intestinal stenosis had poor prognoses.

DISCUSSION: Patients with ischemia in the hepatic flexure and the distal ileum, endoscopic evidence of ulcer or stenosis, higher neutrophil counts, and higher D-dimer levels have worse prognoses. This information could aid in the selection of timely and appropriate treatment.

Clinical and Translational Gastroenterology 2021;12:e00370. <https://doi.org/10.14309/ctg.000000000000370>

INTRODUCTION

Ischemic colitis (IC) is a common form of intestinal ischemic injury. In general, the disease is transient and self-limited. Symptoms and signs of IC can improve within 1–2 weeks of fasting, parenteral nutrition, and even antibiotic treatment. In a few cases, severe consequences such as peritonitis, right colon ischemia, stenosis and necrosis of the colon, renal dysfunction, and *Clostridium difficile* infection associated with high recurrence and mortality rates can occur and may require surgical treatment (1–3). Mortality rates of patients with segmental necrosis range from 20% to 39% (4). Therefore, we have attempted to identify factors influencing IC prognoses during the early stages of the disease.

Colonoscopy is the gold standard for diagnosing IC. Early use of colonoscopy (within 48 hours of symptom onset) reduced mortality, hospital stay lengths, and hospital costs (5). Outcomes of IC seem to depend on several factors, including clinical symptoms, endoscopic ischemic sites, comorbidities, and medications. Previous studies showed that hyperthyroidism, stroke, chronic obstructive pulmonary disease, and complications involving small intestinal lesions might be independent risk factors for high mortality (6,7). Peixoto et al. (8) noted that atrial fibrillation, admission to the intensive care unit, and use of vasopressin drugs were independently associated with inpatient mortality, and a predicted case fatality rate of 32% was observed when all 3 risk factors were present.

Despite these findings, there are no reports presenting both internally and externally validated scoring models with good efficacy for predicting adverse outcomes of IC. Therefore, this study aimed to establish and validate a prognostic scoring model that

could be used to screen patients with IC and identify those requiring intensive treatment or surgery for severe disease in clinical practice.

METHODS

Patients diagnosed with IC by colonoscopy or surgery from November 2008 to May 2020 were identified from the clinical database of Shanghai Changzheng Hospital, Shanghai, China, and Shanghai East Hospital, Shanghai, China (n = 385). This study was approved by the Ethics Review Committee of both hospitals. The process used to select patients for developing the model is shown in Figure 1. Eighty-four patients were excluded, and the internal cohort (n = 260) was enrolled from Shanghai East Hospital. Forty-one patients from Shanghai Changzheng Hospital constituted an external cohort. Severe IC was considered to be present in patients who remained hospitalized for more than 14 days without a clinical cure, those who underwent an open or an interventional surgery, and those who died during hospitalization. Discharge criteria for the included patients were the disappearance of abdominal symptoms and signs, resumption of usual diet, and negative fecal occult blood test results.

Clinical data of all patients were collected during the first 48 hours of admission. Clinical characteristics included age and sex, symptoms, history of abdominal surgery (within the previous month), history of drug use, comorbidities, history of smoking, history of alcohol consumption, laboratory variables, the severity of endoscopic ischemia, and location of the lesion.

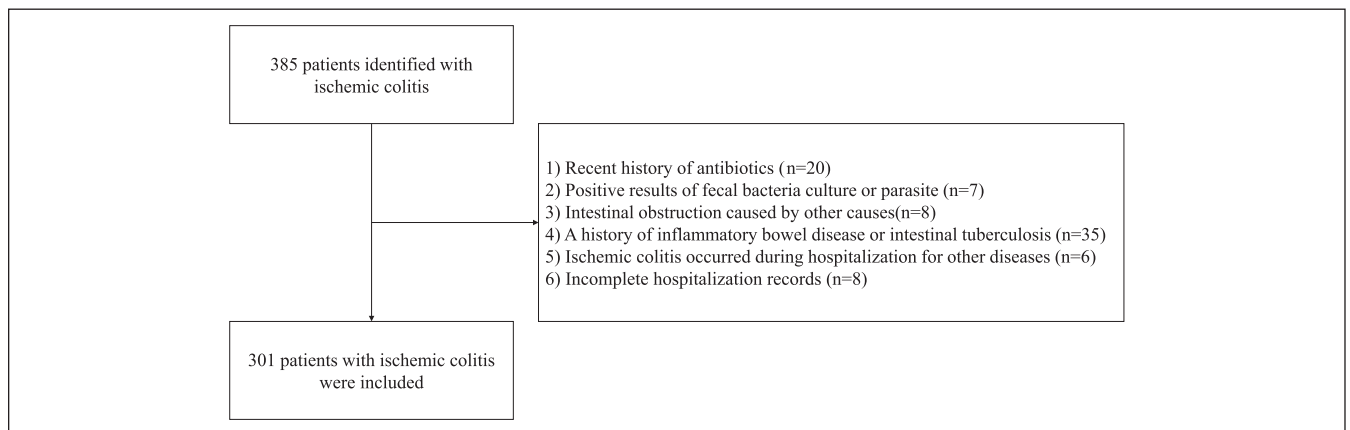


Figure 1. Process used to select the study participants for the prognostic model.

Table 1. Patient characteristics at the baseline

| Variable | Mild (n = 176) | Severe (n = 84) | Statistic | P value |
|--------------------------------------|----------------|-----------------|-----------|---------|
| Sex, n (%) | | | 4.07 | 0.0436 |
| Female | 121 (68.75) | 47 (55.95) | | |
| Male | 55 (31.25) | 37 (44.05) | | |
| Age, yr, n (%) | | | 6.59 | 0.0103 |
| Younger than 65 years | 97 (55.11) | 32 (38.10) | | |
| 65 years or older | 79 (44.89) | 52 (61.90) | | |
| Laboratory findings, n (%) | | | | |
| N > 6.3 × 10 ⁹ /L | 40 (22.73) | 63 (75.00) | 64.95 | <0.0001 |
| PLT < 125 × 10 ⁹ /L | 10 (5.68) | 10 (11.90) | 3.10 | 0.0782 |
| L < 1.1 × 10 ⁹ /L | 27 (15.34) | 29 (34.52) | 12.38 | 0.0004 |
| NLR ≥ 5 | 25 (14.20) | 59 (70.24) | 81.63 | <0.0001 |
| NLR ≥ 7 | 13 (7.39) | 38 (45.24) | 51.67 | <0.0001 |
| NLR ≥ 10 | 3 (1.70) | 21 (25.00) | 36.83 | <0.0001 |
| PLR ≥ 80 | 149 (84.66) | 78 (92.86) | 3.45 | 0.0633 |
| PLR ≥ 100 | 128 (72.73) | 68 (80.95) | 2.07 | 0.1499 |
| PLR ≥ 120 | 92 (52.27) | 56 (66.67) | 4.80 | 0.0284 |
| CRP (mg/L) | | | 58.65 | <0.0001 |
| < 10 | 127 (72.16) | 21 (25.00) | | |
| 10–50 | 37 (21.02) | 33 (39.29) | | |
| > 50 | 12 (6.82) | 30 (35.71) | | |
| WBC count > 9.5 × 10 ⁹ /L | 29 (16.48) | 51 (60.71) | 52.24 | <0.0001 |
| Hb level < 115 (F)/130 (M) g/L | 87 (49.43) | 40 (47.62) | 0.07 | 0.7845 |
| SCr level ≥ 110 (M)/92 (F) μmol/L | 14 (7.95) | 13 (15.48) | 3.46 | 0.0630 |
| LDH level ≥ 250 U/L | 31 (17.61) | 19 (22.62) | 0.92 | 0.3382 |
| Alb level < 35 g/L | 30 (17.05) | 29 (34.52) | 9.90 | 0.0017 |
| BUN level ≥ 7.1 (M)/6.1 (F) mol/L | 11 (6.25) | 18 (21.43) | 13.22 | 0.0003 |
| D-dimer level ≥ 0.55 mg/L | 100 (56.82) | 82 (97.62) | 45.08 | <0.0001 |
| Na ⁺ level < 137 mmol/L | 23 (13.07) | 23 (27.38) | 8.00 | 0.0047 |
| HR > 100 beats/min | 10 (5.68) | 10 (11.90) | 3.10 | 0.0782 |
| Comorbidities, n (%) | | | | |
| Hypertension | 69 (39.20) | 43 (51.19) | 3.33 | 0.0680 |
| Diabetes mellitus | 14 (7.95) | 11 (13.10) | 1.73 | 0.1885 |
| CAD | 37 (21.02) | 21 (25.00) | 0.52 | 0.4713 |
| Atrial fibrillation | 5 (2.84) | 5 (5.95) | 0.77 | 0.3814 |
| COPD | 3 (1.70) | 4 (4.76) | 1.03 | 0.3102 |
| Intestinal surgery | 10 (5.68) | 8 (9.52) | 1.30 | 0.2538 |
| CKD | 2 (1.14) | 2 (2.38) | 0.05 | 0.8229 |
| Stroke | 14 (7.95) | 12 (14.29) | 2.53 | 0.1115 |
| Depression | 6 (3.41) | 0 (0.00) | 1.61 | 0.2039 |
| Hypothyroidism | 3 (1.70) | 1 (1.19) | 0.00 | 1.0000 |
| Hepatitis B | 6 (3.41) | 3 (3.57) | 0.00 | 1.0000 |
| Medications, n (%) | | | | |
| NSAIDs | 18 (10.23) | 10 (11.90) | 0.17 | 0.6832 |
| CCBs | 28 (15.91) | 17 (20.24) | 0.74 | 0.3882 |

Table 1. (continued)

| Variable | Mild (n = 176) | Severe (n = 84) | Statistic | P value |
|----------------------------|----------------|-----------------|-----------|---------|
| β-blockers | 11 (6.25) | 9 (10.71) | 1.60 | 0.2065 |
| ARBs | 31 (17.61) | 10 (11.90) | 1.40 | 0.2375 |
| Lifestyle habits, n (%) | | | | |
| Alcohol consumption | 10 (5.68) | 3 (3.57) | 0.18 | 0.6702 |
| Smoking | 24 (13.64) | 8 (9.52) | 0.89 | 0.3452 |
| Symptoms, n (%) | | | | |
| Stomach ache | 152 (86.36) | 73 (86.90) | 0.01 | 0.9048 |
| Diarrhea | 110 (62.50) | 49 (58.33) | 0.42 | 0.5192 |
| Hematochezia | 140 (79.55) | 63 (75.00) | 0.69 | 0.4074 |
| Vomiting | 41 (23.30) | 26 (30.95) | 1.74 | 0.1868 |
| Constipation | 5 (2.84) | 6 (7.14) | 1.64 | 0.1998 |
| Location, n (%) | | | | |
| Distal ileum | 9 (5.11) | 12 (14.29) | 6.44 | 0.0111 |
| Ascending colon | 7 (3.98) | 20 (23.81) | 24.03 | <0.0001 |
| Hepatic flexure | 7 (3.98) | 18 (21.43) | 19.93 | <0.0001 |
| Transverse colon | 32 (18.18) | 29 (34.52) | 8.46 | 0.0036 |
| Splenic flexure | 40 (22.73) | 32 (38.10) | 6.71 | 0.0096 |
| Descending colon | 89 (50.57) | 47 (55.95) | 0.66 | 0.4163 |
| Sigmoid colon | 111 (63.07) | 40 (47.62) | 5.57 | 0.0182 |
| Rectosigmoid junction | 9 (5.11) | 3 (3.57) | 0.06 | 0.8117 |
| Endoscopic findings, n (%) | | | | |
| Erosion | 84 (47.73) | 37 (44.05) | 0.31 | 0.5780 |
| Ulceration | 41 (23.30) | 45 (53.57) | 23.55 | <0.0001 |
| Stenosis | 6 (3.41) | 42 (50.00) | 82.00 | <0.0001 |
| Necrosis | 0 (0.00) | 10 (11.90) | 18.69 | <0.0001 |
| CTA of SMA | | | | |
| Not evaluated | 96 (54.55) | 35 (41.67) | | |
| No abnormal changes | 42 (23.86) | 17 (20.24) | | |
| Atherosclerosis | 30 (17.05) | 12 (14.29) | | |
| ≤70% stenosis | 8 (4.55) | 7 (8.33) | | |
| >70% stenosis | 0 (0.00) | 4 (4.76) | | |
| Embolism | 0 (0.00) | 9 (10.71) | | |

Alb, albumin; ARBs, angiotensin receptor blockers; BUN, blood urea nitrogen; CAD, coronary artery disease; CCBs, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CTA, computed tomography angiography; F, female; Hb, hemoglobin; HR, heart rate; L, lymphocyte count; LDH, lactate dehydrogenase; M, male; N, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; SCR, serum creatinine; SMA, superior mesenteric arteriography; WBC, white blood cell.

All variables are divided into categorical variables (Table 1). Quantitative variables were divided into 2 groups bounded by their normal upper or lower limits. This classification helped clinicians to visually identify variable groups with high statistical significance. We showed the benefits of dichotomous variables by using a nomogram (Figure 2).

Statistical analysis

Univariate analysis. Continuous variables were expressed as the mean ± SD or as the median (interquartile range) based on the

data distribution. The independent-samples *t* test or Wilcoxon rank-sum test were used for comparisons. Categorical data were described as the frequency (percentage). Comparisons between the 2 groups were performed using the χ^2 test or Fisher exact test.

Development of the prognostic model. Variables with $P < 0.05$ according to the univariate analysis were selected for inclusion in the multivariate logistic regression analysis. The stepwise method was used to select the variables. The entry criterion was $P < 0.1$, and the exclusion criterion was $P > 0.1$. A nomogram was used to

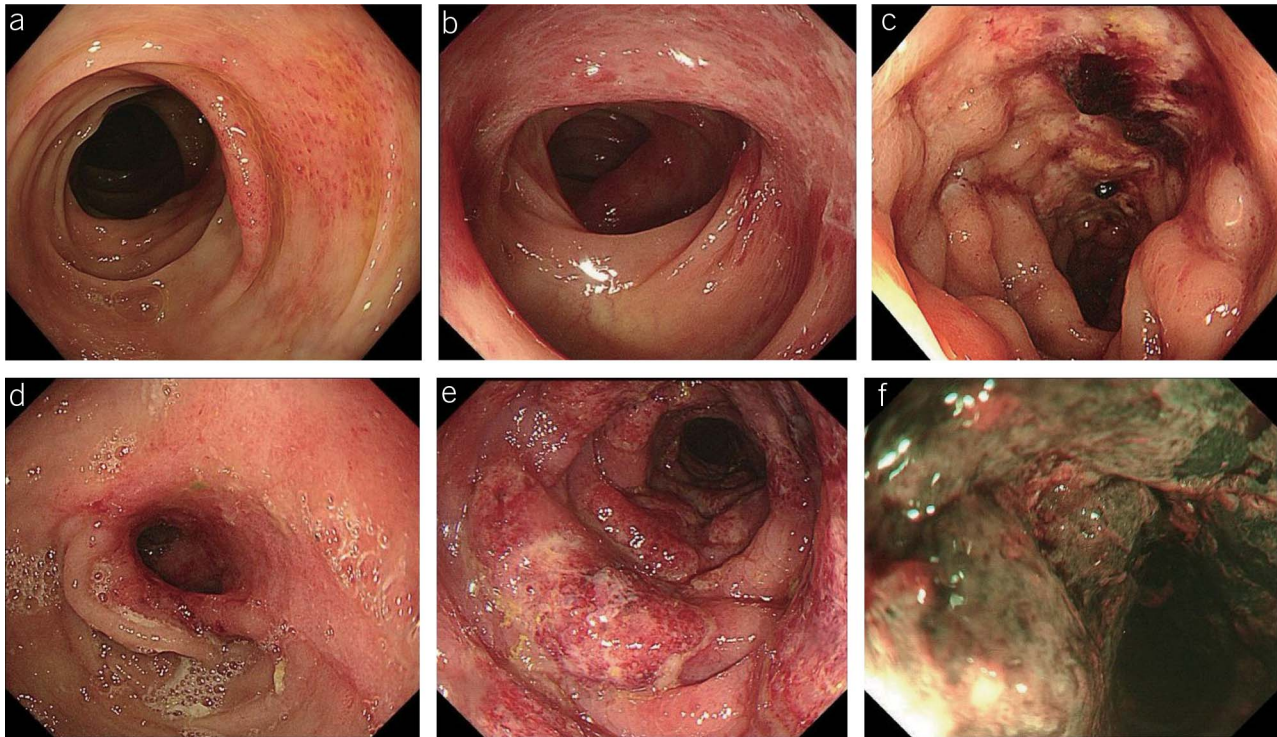


Figure 2. Endoscopic findings of patients with mild IC and those who were critically ill. (a) Local hyperemia and edema of the intestinal mucosa. (b) Erosion of intestinal mucosa. (c) Deep linear ulceration along the longitudinal axis of the colon. (d) Enteric stenosis through which the endoscope cannot be passed. (e) Extensive mucosal necrosis. (f) Coexistence of the aforementioned ischemic manifestations. Image courtesy of the Endoscopy Center, Shanghai East Hospital, China.

construct a prediction model based on the results of the multivariate logistic regression analysis.

Internal cross-validation and external validation. In this study, 5-fold cross-validation was used as the internal validation method. A subset containing 80% of the cohort was randomly selected for training. The remaining 20% were selected for testing. The cross-validation process was repeated 5 times. External validation was performed using data from Shanghai Changzheng Hospital. Sensitivity, specificity, accuracy, Youden index, kappa coefficient, and areas under the receiver-operating characteristic curves (AUROCs) were used to evaluate the predictive ability of the model. All tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

All statistical analyses and data management were performed using SAS version 9.4 (SAS Institute, Cary, NC). The nomogram was constructed using the rms package in R software version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and clinical characteristics at baseline

Two-hundred sixty patients (168 women) with a mean age of 64.5 ± 12.2 years (range, 24–91 years) with IC were enrolled in the internal cohort. Fourteen patients underwent interventional/surgical procedures, and 3 patients died postoperatively. The mortality rate within 2 weeks of hospitalization was 2.6%. Demographic and clinical characteristics of patients with different outcomes are summarized in Table 1. Clinical details of quantitative variables are shown in Table 2.

Patients usually presented with abdominal pain (86.5%), rectal bleeding (78.1%), diarrhea (61.2%), vomiting (25.8%), or

constipation (4.2%). More than one-third of the patients ($n = 112$; 43.1%) had essential hypertension; other patient conditions included coronary heart disease ($n = 58$; 22.3%), cerebrovascular disease ($n = 26$; 10%), diabetes ($n = 25$; 9.6%), and a recent history of intestinal surgery ($n = 18$; 6.9%). A few patients had been treated with nonsteroidal anti-inflammatory drugs (NSAIDs) ($n = 28$; 10.8%), calcium channel blockers ($n = 45$; 17.3%), β -blockers ($n = 20$; 7.7%), or angiotensin receptor blockers ($n = 41$; 15.8%).

The progression of ischemia according to colonoscopy results is shown in Figure 2. Ischemic changes were found in the distal ileum (8.1%), ascending colon (10.4%), hepatic flexure (9.6%), transverse colon (23.5%), splenic flexure (27.7%), descending colon (52.3%), sigmoid colon (58.1%), and rectosigmoid junction (4.6%). In some patients, ischemia extended to more than 2 colon segments or even the entire colon. Young people were less susceptible to IC. A total of 9 young patients (<40 years old) with IC were enrolled in this study; 55% of them were men. Their mean age was 32 years (range, 24–38 years). Eight patients developed the disease in the left colon and one in the right colon, and all received symptomatic therapy.

Only 129 patients underwent computed tomography (CT) angiography of the superior mesenteric artery. Approximately 45.7% of these patients showed negative results, and the other patients showed different degrees of atherosclerosis, stenosis, or even embolism.

Prognostic nomogram

Univariate predictors of the prognosis of IC are shown in Table 1. After performing purposeful stepwise regression in the multivariate analysis, 6 predictors were obtained: neutrophil count $> 6.3 \times 10^9/L$, D-dimer level ≥ 0.55 mg/L, ischemia of the distal

Table 2. Detailed clinical features of the internal cohort of ischemic colitis

| Variable | Mild (n = 176) | Severe (n = 84) |
|---------------------------------|----------------|-----------------|
| Age (yr) | 62.89 ± 11.69 | 67.73 ± 12.61 |
| N (×10 ⁹ /L) | 4.72 ± 2.44 | 8.88 ± 3.68 |
| PLT (×10 ⁹ /L) | 207.18 ± 68.06 | 197.60 ± 62.82 |
| L (×10 ⁹ /L) | 1.65 ± 0.59 | 1.37 ± 0.61 |
| CRP level (mg/L) | 13.44 ± 20.89 | 50.95 ± 59.42 |
| WBC count (×10 ⁹ /L) | 6.82 ± 2.80 | 11.04 ± 3.97 |
| Hb (g/L) | 127.32 ± 16.49 | 122.21 ± 23.09 |
| NLR | 3.32 ± 2.85 | 8.61 ± 8.27 |
| PLR | 142.20 ± 78.90 | 183.94 ± 143.14 |
| SCr level (μmol/L) | 72.38 ± 16.34 | 78.08 ± 30.36 |
| LDH level (U/L) | 202.66 ± 82.68 | 243.89 ± 170.52 |
| Alb level (g/L) | 40.03 ± 4.95 | 36.02 ± 6.08 |
| BUN level (mmol/L) | 4.16 ± 1.45 | 5.53 ± 3.39 |
| D-dimer level (mg/L) | 0.93 ± 0.83 | 3.30 ± 3.54 |
| Na ⁺ level (mmol/L) | 140.55 ± 3.34 | 139.11 ± 4.46 |
| LOS (d, median–IQR) | 8 (6–11) | 16 (15–19) |

Alb, albumin; BUN, blood urea nitrogen; CRP, C-reactive protein; Hb, hemoglobin; IQR, interquartile range; L, lymphocyte count; LDH, lactate dehydrogenase; LOS, length of stay; N, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SCr, serum creatinine; WBC, white blood cell.

ileum, ischemia of the hepatic flexure, ulceration, and luminal stenosis (Table 3). The model is presented as a nomogram in Figure 3. All variables were set as binary for easy calculation.

Validation and performance of the nomogram

The final logistic regression model had high overall accuracy for predicting the prognosis, with an AUROC of 0.86 (Table 4). In the external validation cohort, 26.8% (11/41) of the patients were defined as having poor prognoses. The model showed good discrimination ability during external validation, with an AUROC of 0.95, which was even better than the internal validation results. Regardless of the verification method used, the kappa coefficient was highly consistent with the predicted results of the model and the actual classification results.

Subgroup multivariate analysis

To further explore whether there were differences in prognostic predictors across age groups, subgroup analyses were performed by combining internal and external cohorts and separating them into patients older and younger than 65 years. The factors for poor prognoses were different between patients older than 65 years and younger than 65 years. More details are shown in Table 5 and Table 6.

Similarly, to further compare the differences in prognosis between patients with left and right colon involvement, the 2 groups of patients with different outcomes were further divided into 3 subgroups. The grouping criteria for subgroup analysis were left colon, right colon, and both left and right colon.

Table 3. Multivariate logistic regression analysis of patients with ischemic colitis and poor disease prognoses

| Variable | OR (95% CI) | P value |
|--|------------------------|---------|
| Neutrophil count >6.3 × 10 ⁹ /L | 14.168 (4.986–40.264) | <0.0001 |
| D-dimer level ≥0.55 mg/L | 47.206 (6.905–322.706) | <0.0001 |
| Distal ileum | 25.464 (5.06–128.142) | <0.0001 |
| Hepatic flexure | 29.9 (6.308–141.738) | <0.0001 |
| Ulceration | 2.534 (1.073–5.984) | 0.0339 |
| Luminal stenosis | 37.954 (10.518–136.95) | <0.0001 |

CI, confidence interval; OR, odds ratio.

Multivariate analysis of the left colon subgroup showed that higher neutrophil count, higher D-dimer level, higher neutrophil-to-lymphocyte ratio (NLR), and colon stenosis were associated with poor prognoses (Table 7). However, because of the small number of patients in the other 2 groups, the model results could not be obtained.

DISCUSSION

Laboratory examination or colonoscopy alone was insufficient to adequately assess prognoses. A comprehensive predictive model can be used for the early, rapid, and quick assessment of prognosis. We developed such a model using retrospective, high-quality, and multicenter data. To facilitate practical use, the model was constructed using 2 laboratory variables and 4 variables observed during colonoscopy. We found that poor prognoses in patients aged 65 years and older were mainly related to the colonic ischemic site. Poor outcomes in patients younger than 65 years were mainly associated with abnormal laboratory indicators. The accuracy and reproducibility of the model were validated both internally and externally. To the best of our knowledge, currently, this model is the only one that has been validated internally and externally to predict poor prognoses in patients with IC.

An earlier study using a predictive model found that tachycardia, shock within 24 hours of admission, and ulcers found on endoscopy were independent predictors of poor prognoses. The probability and risk index for severe IC for patients with all 3 risk factors were 74-times higher than those for patients without risk factors (9). Sun et al. (10) identified the following possible predictors of poor prognoses: male sex, tachycardia, no rectal bleeding, peritonitis, hypotension (systolic blood pressure <90 mm Hg), and isolated right colonic ischemia. Pastor et al. (11) established a prognostic model combining ultrasonographic and clinical manifestations, including pain, diarrhea, rectal bleeding, hypertension, and pericolic fat changes. The evidence for these models is insufficient because of a lack of external validation. Moreover, it is difficult to compare mild and severe cases because of the different classification criteria of each model.

Partly in line with previous studies, we found evidence of ulceration and right colonic ischemia as predictors of poor prognosis. The difference is that the previous model did not include laboratory variables, which our study did. In addition to large sample size and a comprehensive collection of clinical data, most prognostic factors mentioned in previous studies were included in this study. However, evidence of endoscopic mucosal necrosis was not included in the model because necrosis is

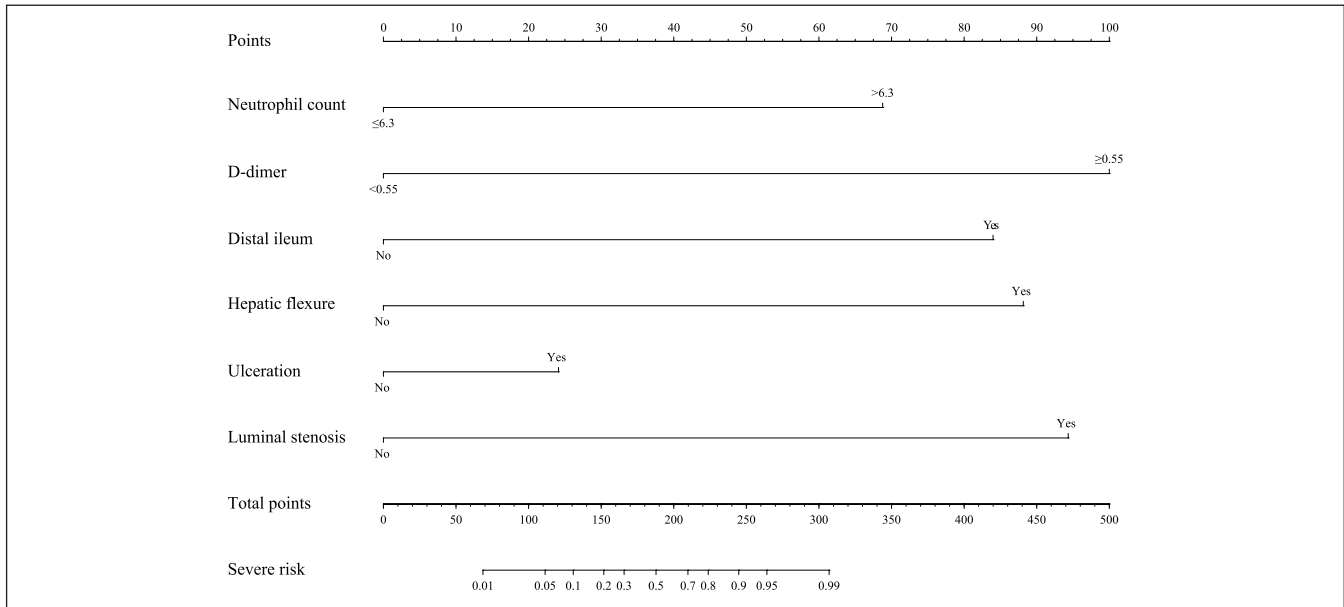


Figure 3. A nomogram was constructed based on 6 clinical parameters. The length of the line segment corresponding to each variable reflects the contribution of this factor to the outcome. The points at the top of the graph represent the scores for each variable with different values. The total points represent the sum of the individual scores of all variables. The severe risk value corresponding to the total points is the probability of the occurrence of the event.

inherently an indicator of poor prognosis and the urgent need for surgery. This study shows that when the evidence of colonic necrosis is not clear, clinicians can use our model to determine which patients need more attention and strengthen treatment. We also designed dichotomous variables and a nomogram to facilitate the clinical application of the model. An easy-to-understand nomogram can be used to predict the risk of poor prognoses without memorizing the formula.

In this study, ischemic sites were identified based on detailed considerations. Consistent with previous studies (3,6,12), right colon ischemia was strongly associated with poor prognosis in this study. Evidence of ischemia in the terminal ileum and ascending colon was incorporated into the predictive model. Other studies have generally mentioned different signs and causes of left and right colon ischemia, but so far, we have not seen a prognostic model based on the location of ischemia. In our study, subgroup analysis of the patients with left colon involvement showed that neutrophil count, NLR, D-dimer level, and evidence of colon stenosis were all associated with poor prognoses. Right colon

subgroup analysis was not possible because of the small number of patients.

Elderly patients are prone to IC, which is often accompanied by some primary diseases. Widely reported diseases associated with IC include cardiovascular and cerebrovascular diseases (such as coronary heart disease, arrhythmia, and stroke), hypertension, diabetes, infections (e.g., *Escherichia coli* and hepatitis B virus infections), pancreatitis, vasculitis, and irritable bowel syndrome (10,13). In a study of IC in young adults, 21% of patients younger than 40 years had a history of an autoimmune disease such as systemic lupus erythematosus or vasculitis (4). In our study, the incidence of comorbidities in elderly patients was similar to that previously reported (10,13). Among people younger than 40 years, the underlying diseases were chronic gastritis (n = 2), fatty liver (n

Table 4. Model performance parameters

| | Internal 5-fold cross-validation (n = 260) | External validation (n = 41) |
|-------------------|---|---------------------------------|
| Sensitivity | 84.52% | 100% |
| Specificity | 89.77% | 97% |
| Correct rate | 88.08% | 98% |
| Youden index | 0.7429 | 0.9677 |
| AUC | 0.8609 | 0.9545 |
| Kappa coefficient | 0.7316 (0.6434–0.8192) | 0.9360 (0.8125–1.0000) |

AUC, area under the curve.

Table 5. Multivariate analysis of a subgroup of patients younger than 65 years

| Variable | Regression coefficient | SE | OR (95% CI) | Wald χ^2 | Pvalue |
|--|------------------------|------|--------------------|---------------|--------|
| Intercept | 5.71 | 1.53 | | 13.85 | 0.0002 |
| N \leq 6.3 \times 10 ⁹ /L | -1.91 | 0.69 | 0.15 (0.04–0.58) | 7.60 | 0.0058 |
| NLR <5 | -2.11 | 0.60 | 0.12 (0.04–0.39) | 12.36 | 0.0004 |
| D-dimer <0.55 mg/L | -2.87 | 1.15 | 0.06 (0.01–0.54) | 6.22 | 0.0126 |
| Ascending colon | 2.48 | 1.03 | 12.05 (1.58–90.91) | 5.76 | 0.0164 |
| HR \leq 100 beats/min | -2.34 | 0.97 | 0.10 (0.02–0.64) | 5.83 | 0.0157 |

CI, confidence interval; HR, heart rate; N, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

Table 6. Multivariate analysis of a subgroup of patients aged 65 years and older

| Variable | Regression coefficient | SE | OR (95% CI) | Wald χ^2 | P value |
|--|------------------------|------|---------------------|---------------|---------|
| Intercept | 7.27 | 1.62 | | 20.27 | <0.0001 |
| N \leq 6.3 \times 10 ⁹ /L | -2.01 | 0.48 | 0.134 (0.052–0.346) | 17.33 | <0.0001 |
| D-dimer level <0.55 mg/L | -4.1 | 1.23 | 0.02 (0.00–0.18) | 11.17 | 0.0008 |
| Distal ileum | 2.12 | 0.92 | 8.33 (1.37–50.00) | 5.30 | 0.0213 |
| Hepatic flexure | 2.64 | 0.92 | 14.08 (2.34–83.33) | 8.34 | 0.0039 |
| Splenic flexure | 1.22 | 0.50 | 3.39 (1.27–9.09) | 5.96 | 0.0146 |
| Stenosis | 1.31 | 0.57 | 3.70 (1.21–11.36) | 5.28 | 0.0216 |

CI, confidence interval; N, neutrophil count; OR, odds ratio.

= 2), and hepatitis B (n = 2). We did not find associations between these comorbidities and poor prognoses of IC.

The predisposing factors for IC reported in the literature include medications, colonoscopy, trauma, pancreatitis, hypovolemia, alcohol abuse, abdominal or aortic surgery, and long-distance running (14). The administration of an enema and colonoscopy performance may increase the pressure on the bowel, thus leading to bowel ischemia (5). Removal of a malignant tumor from the colon may reduce the blood supply to the surrounding intestine (15). Similarly, the occurrence of IC in some patients in our study was caused by definite causes: partial colon resection for colon cancer (n = 18), colonoscopy (n = 3), running (n = 1), and trauma (n = 1). However, there was no clear association between these triggers and poor prognoses.

The use of certain drugs has been an increasing focus of attention as a risk factor for IC. In the literature on pharmacological causes of colonic ischemia, psychotropic medications, NSAIDs, digitalis, agents that cause constipation or diarrhea, hormones, and tumor necrosis factor-alpha inhibitors had the strongest associations with IC (16). A national cohort study showed that β -blockers, opioids, and NSAIDs increase the risk of IC (17). In this study, the most commonly used drugs for patients before admission included NSAIDs, β -blockers, calcium channel blockers, and angiotensin receptor blockers. The univariate analysis showed that these drugs were not associated with the prognosis of IC. Opioids are tightly controlled in China and are only used for anesthesia and severe pain. None of the patients in this study took opioids, so its use is not comparable with that in other studies.

The severity and prognoses of IC have been associated with some laboratory variables. Some studies showed that patients with severe IC had elevated white blood cell counts, higher than normal blood urea nitrogen and lactate dehydrogenase levels, and lower albumin and hemoglobin levels (1,18,19). The univariate analysis in this study showed that patients with severe IC had lower albumin levels, lymphocyte count, serum sodium content, and higher levels of D-dimer, neutrophils, blood urea nitrogen, and C-reactive protein. In the end, only neutrophil count and D-

Table 7. Multivariate analysis of the left colon subgroup

| Variable | Regression coefficient | SE | OR (95% CI) | Wald χ^2 | P value |
|--|------------------------|------|------------------|---------------|---------|
| Intercept | 0.26 | 0.28 | | 0.80 | 0.3714 |
| N \leq 6.3 \times 10 ⁹ /L | -1.40 | 0.43 | 0.25 (0.11–0.57) | 10.65 | 0.0011 |
| D-dimer level <0.55 mg/L | -2.44 | 0.76 | 0.09 (0.02–0.39) | 10.27 | 0.0013 |
| NLR <5 | -1.02 | 0.42 | 0.36 (0.16–0.82) | 5.91 | 0.0151 |
| Stenosis | 1.12 | 0.44 | 3.06 (1.28–7.31) | 6.33 | 0.0094 |

CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

dimer level were included in the prediction model. In the subgroup of patients younger than 65 years, heart rate > 100 beats per minute also suggested a poor prognosis.

The NLR and platelet-to-lymphocyte ratio have been widely used as readily available inflammatory indicators to assess the severity and prognoses of cardiovascular disease, cancer, and gastrointestinal disease (15,20–23). A high NLR has been shown to be an independent predictor of death from coronary artery disease, acute coronary syndrome, and congestive heart failure (23). During the univariate analysis, we found that the NLR was statistically significant when classified by multiple criteria (NLR \geq 5/7/10) but that the platelet-to-lymphocyte ratio was only statistically significant when bound by a value of 120. None of them were included in our prognostic model. However, NLR \geq 5 was statistically significant in the multivariate subgroup analysis for individuals younger than 65 years and with left colon involvement.

Ultrasonography is of limited value for imaging IC because gases in the hollow organs can interfere with the clinician's judgment. Changes in pericolic fat and colitis may indicate sonographic manifestations of severe colonic ischemia (11). CT findings of patients with IC may include deposition of mesenteric fat, thickening of the intestinal wall, and abnormal strengthening of the contrast of the intestinal wall; however, these findings were independent of disease severity (24). In this study, too few patients underwent abdominal ultrasonography and CT, so these data were not included. However, nearly half of the patients underwent CT angiography, and we found that patients with poor outcomes had more severe atherosclerosis, with only 17 patients having normal results.

This study also had some limitations. First, we did not collect follow-up data after discharge. Second, we noticed that decreases in hemoglobin and bicarbonate levels or increases in white blood cell or lactate dehydrogenase levels during hospitalization were frequently seen in patients with severe IC (1). However, changes in laboratory variables were not included in our prediction model. Owing to the limitations of the retrospective study, we were unable to perform any interventions. Many patients with good outcomes had undergone only one blood test, so we did not have laboratory parameters for all patients 48 hours after hospitalization and could not compare them further. Therefore, larger sample sizes and more detailed data on changes in laboratory variables during hospitalization are needed in the future to obtain more accurate models of future mortality projections.

In conclusion, we developed a nomogram-based prognostic model, based on a multicenter, retrospective, and real-world data, to evaluate predictors of poor prognoses in patients with IC. This

model was confirmed to have good internal and external validity. This model can enable identification of patients with poor prognosis and those who will require long hospitalization time and excessive medical resources to allow for early intervention and avoid adverse consequences. The improvement of the model requires a larger sample size and more data on changes in variables during hospitalization.

CONFLICTS OF INTEREST

Guarantor of this article: Lan Zhong, MD.

Specific author contributions: Yiwei Luo, MM has equal rights with the first author Shan Li, MB, and Junyi Han, MD has equal rights with the corresponding author Lan Zhong, MD. Study concept and design: S.L. and L.Z. Acquisition of data: Y.L., W.W., and X.Y. Analysis and interpretation of data: S.L., J.L., M.H., J.H., and Q.S. Manuscript writing: S.L., J.L., Y.L., W.W., X.Y., M.H., Q.S., and L.Z. Analysis and interpretation of the data: X.Y. All authors approved the final draft submitted.

Financial support: This work was funded by Technology Development Project of Pudong Science, Technology and Economic Commission of Shanghai (Grant No. PKJ2017-Y17), Key Specialty Construction Project of Pudong Health and Family Planning Commission of Shanghai (Grant No. PWZk2017-26) and The Top-Level Clinical Discipline Project of Shanghai Pudong (PWYgf2018-04). The authors received research funding in statistics and publishing.

Potential conflicts of interest: None to report.

Informed consent: Informed consent was obtained from all study participants.

ACKNOWLEDGMENT

The authors thank Yibin Guo for his help with the statistical analysis.

Study Highlights

WHAT IS KNOWN

- ✓ Severe ischemic colitis (IC) patients have higher recurrence and mortality rates than mild colitis patients.
- ✓ There is no scoring model with both internal and external validation to predict poor outcomes.

WHAT IS NEW HERE

- ✓ We developed a nomogram-based prognostic model for patients with IC.
- ✓ Patients with ischemia in the hepatic flexure and distal ileum had a poor prognosis.
- ✓ Patients with endoscopic evidence of ulcer or stenosis had a poor prognosis.
- ✓ Patients with a higher blood neutrophil count and serum D-dimer level had a poor prognosis.
- ✓ The poor prognosis of patients aged 65 years and older was related to the colonic ischemia site.
- ✓ The poor prognosis of patients younger than 65 years was associated with abnormal laboratory indicators.

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