



A Multi-marker Model Based on Routine Laboratory Parameters for Predicting Intestinal Fibrosis in Crohn's Disease

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Abstract: Background: This study aimed to evaluate the diagnostic value of complete blood count, biochemical, and coagulation parameters in identifying intestinal fibrosis in patients with Crohn's disease. Methods: A retrospective study was conducted, including 280 patients with intestinal fibrosis and strictures due to Crohn's disease from the Sixth Affiliated Hospital of Sun Yat-sen University as the case group, and 104 patients with benign intestinal diseases as the control group. ROC curve analysis was performed to evaluate the performance of each individual laboratory parameter. Finally, a multi-parameter combination with a high area under the receiver operating characteristic curve (AUC), high sensitivity, and high specificity was selected to assess its predictive diagnostic performance for intestinal fibrosis and strictures in Crohn's disease. Results: Among the 35 laboratory parameters evaluated, eight highly predictive biomarkers were identified—each exhibiting an AUC > 0.70 and a statistically significant P-value < 0.0001. Fasting glucose (GLU) demonstrated the strongest discriminative performance (AUC = 0.7683). Predictive models integrating multiple biomarkers significantly outperformed single-biomarker models in diagnostic accuracy. A total of 226 combinatorial models were constructed; the optimal 8-biomarker model achieved an AUC of 0.9197. Following systematic elimination of redundant features, a parsimonious 5-biomarker model—comprising fasting glucose (GLU), mean corpuscular volume (MCV), platelet distribution width-standard deviation (PDW-SD), activated partial thromboplastin time (APTT), and lymphocyte count (LYM)—yielded an AUC of 0.9169. This value was not significantly different from that of the 8-biomarker model ($\Delta\text{AUC} = 0.0028$; $P > 0.05$), indicating comparable diagnostic accuracy and strong translational potential for clinical implementation. Conclusion: This study assessed the predictive value of 35 routine complete blood count, biochemical, and coagulation parameters for intestinal fibrosis in Crohn's disease, identified eight parameters with robust diagnostic performance, and developed a multi-parameter predictive model. A five-marker combination—GLU, MCV, PDW-SD, APTT, and LYM—was ultimately determined to be the optimal non-invasive predictive tool. Future studies may integrate novel molecular biomarkers associated with fibrogenesis to further enhance prediction accuracy.

Keywords: Crohn's disease, intestinal fibrosis, intestinal stenosis, laboratory parameters, non-invasive prediction

INTRODUCTION

Crohn's disease is a chronic, nonspecific inflammatory bowel disease (IBD) of unknown cause. It usually follows a prolonged, relapsing course and is difficult to cure completely. Its incidence is rising steadily worldwide, with the highest prevalence among young adults aged 15-25. Lesions can occur discontinuously anywhere along the gastrointestinal tract, but most often affect the terminal ileum and colon. During active disease, common symptoms include abdominal pain, diarrhea, rectal bleeding, oral ulcers, and weight loss. Intestinal strictures and obstructions caused by fibrous tissue proliferation in the bowel wall are major complications and the main reasons patients require repeated surgery. Early detection of complications such as intestinal strictures and fibrosis is essential for reducing the need for surgery and improving patients' quality of life. In clinical practice, the diagnosis and assessment of Crohn's disease mainly rely on endoscopy, imaging, and histopathological examination. However, endoscopy is invasive, uncomfortable for patients, and relatively costly, which limits its use for frequent, dynamic disease monitoring. Although no specific biomarkers are currently available for diagnosis or disease assessment, some biomarkers do change as the disease progresses. Nevertheless, due to their limited sensitivity and specificity, relying solely on these markers to evaluate disease status is unreliable and may lead to misdiagnosis or missed diagnoses.

According to the current state of research, most existing studies have focused on the combined application of inflammation assessment with routine laboratory tests. Hematologic measures, including complete blood count, inflammatory markers, nutritional status, and coagulation function, are often used to assess disease activity and predict complications. Therefore, these indicators can indirectly reflect the possibility of intestinal fibrosis and stenosis. However, these measures only reflect the current inflammatory state and cannot predict the progression of fibrosis after inflammation has resolved. Studies on specific laboratory markers of fibrosis in Crohn's disease are still limited ^[1,2]. In addition, pathological diagnostic criteria have not clearly defined the prefibrotic features of intestinal tissue remodeling. Techniques such as endoscopic ultrasonography and magnetic resonance imaging can detect established fibrosis but cannot predict its progression. Therefore, we need new methods to distinguish between inflammation and fibrosis. However, quantitative methods to assess fibrosis remain to be refined, which limits the clinical applicability of existing studies^[3]. Geng et al. found that intestinal adipocytes can differentiate into myofibroblast-like cells in a chronic inflammatory environment, directly promoting fibrosis, and providing a potential target for blood-based biomarker development. ^[4] A study by Huang et al. confirmed that thrombocytocrit (PCT), platelet-to-lymphocyte ratio (PLR), and albumin (ALB) were independent predictors of disease activity in Crohn's disease. Combined with the Harvey-Bradshaw Index (HBI), it provides a non-invasive and effective clinical assessment tool ^[5]. Wang et al. evaluated a model incorporating blood markers and computed tomographic enterography (CTE) scores. The AUC values of remission stage, mild active stage and moderate to severe active stage were 0.983, 0.852 and 0.917, respectively. The mean AUC of the log-linear model consisting of gender, radiomics score, and serum score was 0.940 ^[6]. At present, evaluation continues to rely primarily on imaging, endoscopic, and pathological examinations following clinical diagnosis. Blood biomarkers are used mainly to monitor inflammation, but they remain limited in their ability to distinguish fibrosis from stenosis. Although research has begun to focus on more specific serum biomarkers, these studies still require further refinement ^[7]. Research on DNA

methylation-based prediction is also at an early stage. Multicenter genome-wide association studies are lacking, and most existing studies rely on small samples and targeted screening, with few models tailored to specific drugs^[8]. Systematic efforts have examined serological, genetic, and histopathological biomarkers of intestinal strictures and fibrosis in Crohn's disease, and some have shown a degree of predictive value^[9]. However, few biomarkers have been validated in multicenter studies or are ready for clinical use. Standardized thresholds for radiological assessment are also lacking. In addition, reliable tools for accurate prediction remain unavailable, making personalized risk stratification challenging^[10]. The development of a convenient, efficient, and accurate indicator for early prediction of intestinal fibrosis has therefore become an urgent clinical need and provides an important rationale for the present study.

This study examines common, readily available routine laboratory measures, including complete blood counts, a six-item biochemical panel, and coagulation tests. It compares these parameters in patients with Crohn's disease-related intestinal fibrosis and strictures with those in a control group of patients with benign intestinal diseases. ROC curves will then be used to identify combinations of parameters with high AUC values. The aim is to develop a noninvasive diagnostic protocol and identify early warning markers, providing primary care settings with a standardized tool for initial screening. This approach may help overcome the limitations of invasive examinations and the poor diagnostic performance of individual markers, improve early detection, reduce the need for surgery, and support more precise diagnosis and further research on Crohn's disease.

MATERIALS AND METHODS

General information

This study included 280 patients with Crohn's disease-associated intestinal strictures and accompanying fibrosis who were diagnosed by endoscopy and pathology at the Sixth Affiliated Hospital of Sun Yat-sen University between January 2020 and October 2025. A control group of 104 patients with benign intestinal diseases who underwent surgical resection at the same hospital during the same period was simultaneously included. Clinical data (including age, sex, disease duration, endoscopic and pathological characteristics, and complications) as well as laboratory data, including 23 complete blood count parameters, coagulation function tests, and six biochemical parameters, were retrospectively collected and analyzed for both groups. ROC curve analysis and statistical analyses were used to identify a high-performance, multi-indicator combination for predicting intestinal fibrosis in Crohn's disease, thereby providing a basis for the noninvasive and precise prediction of intestinal fibrosis and strictures in this condition. The study population encompassed different age groups (children, adults, and the elderly) and both sexes, including outpatients and inpatients from the Sixth Affiliated Hospital of Sun Yat-sen University, and was divided into a case group and a control group.

Inclusion and Exclusion Criteria

Inclusion Criteria

Inclusion criteria for the case group were as follows: (1) participants spanned all age groups-children, adults, and the elderly-with no sex restrictions; (2) they had a definitive diagnosis

of Crohn's disease-related intestinal strictures with intestinal fibrosis confirmed by endoscopy combined with histopathological examination; and (3) they had completed relevant laboratory tests, including a complete blood count and coagulation function tests, prior to surgery. Inclusion criteria for the control group were as follows: patients diagnosed with benign intestinal diseases at the same hospital during the same period. Both groups included outpatients and inpatients. Laboratory test samples met predefined quality standards, and patients' baseline information, clinical records, and relevant test data were complete and verifiable.

Exclusion Criteria

Exclusion criteria were as follows: (1) patients who did not meet the diagnostic criteria for Crohn's disease-associated intestinal strictures with intestinal fibrosis or the selection criteria for the benign disease control group; (2) patients with concomitant conditions that could affect study results, such as infectious bowel disease, severe hepatic or renal insufficiency, or malignant tumors; (3) patients referred to the study hospital after having been diagnosed with Crohn's disease-associated intestinal strictures with intestinal fibrosis or a benign condition at another hospital; and (4) patients whose laboratory test samples did not meet quality standards or whose test results were missing.

Methods

Venous blood samples were collected from all study participants under fasting conditions, strictly in accordance with clinical laboratory specimen collection standards, and pre-analytical processing was performed as required by the test protocol.

The 23-parameter complete blood count (CBC) was performed on a Mindray CAL 8000 fully automated hematology analyzer, which uses impedance technology combined with laser flow cytometry for whole-blood cell counting and differentiation. The parameters measured included white blood cell count (WBC), absolute neutrophil count (NEU), absolute lymphocyte count (LYM), absolute monocyte count (MONO), absolute eosinophil count (EOS), absolute basophil count (BASO), neutrophil percentage (NEU%), lymphocyte percentage (LYM%), monocyte percentage (MONO%), eosinophil percentage (EOS%), basophil percentage (BASO%), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width coefficient of variation (RDW-CV), red blood cell distribution width standard deviation (RDW-SD), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT).

The six-item biochemical panel was performed using a Beckman Coulter AU5800 fully automated biochemical analyzer, which employs a colorimetric method to measure each biochemical parameter. The parameters tested were: potassium (K), sodium (Na), chloride (Cl), calcium (Ca), inorganic phosphorus (P), and glucose (GLU). The coagulation function was detected by Mindray MT8000 automatic coagulation analyzer. The parameters included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), and quantitative D-dimer (DD).

All assays were conducted only after instrument calibration was verified and internal quality control criteria were satisfied. Procedures strictly adhered to the manufacturers' standard operating procedures and the reagent kit's instructions for use. Test results were interpreted using the laboratory's validated reference intervals to ensure analytical accuracy and clinical reliability.

Statistical Analysis

Statistical analyses were performed, and graphs were generated, using SPSS 22.0, Excel, and GraphPad Prism 6.07. Normally distributed continuous variables are presented as mean $\pm$ standard deviation, whereas non-normally distributed variables are presented as median (interquartile range). Intergroup comparisons were performed using the Mann-Whitney U test, with results presented as Z-scores and P-values; categorical variables were expressed as percentages. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

ROC Curve Analysis of Laboratory Parameters

ROC curve analysis was used to evaluate the predictive performance of complete blood count, six biochemical parameters, and coagulation function indicators for intestinal fibrosis in Crohn's disease, with the AUC as the primary quantitative criterion (screening threshold: $AUC > 0.70$ for individual indicators). Candidate indicators were selected based on statistical significance ($\alpha = 0.05$). Among the 35 laboratory indicators included in the analysis, there were large differences in the diagnostic efficacy of each indicator, and the differences were statistically significant ($P < 0.0001$). Only 8 of these markers met the screening criteria of $AUC > 0.70$ and were therefore classified as high-value candidate diagnostic markers.

GLU ($AUC = 0.7683$) showed the best diagnostic performance. Abnormal GLU levels are associated with metabolic disturbances and impaired intestinal absorption caused by chronic inflammation in Crohn's disease, and may serve as an indirect early indicator of disease progression. Abnormal MCV ($AUC = 0.7651$) and HCT ($AUC = 0.7590$) are associated with malabsorption and chronic anemia resulting from prolonged intestinal inflammation, and may help assess disease severity. An abnormally elevated PDW ($AUC = 0.7551$) increases platelet activation and may contribute to intestinal fibrosis. APTT ($AUC = 0.7490$) reflects abnormalities in the intrinsic coagulation pathway and is associated with inflammation-mediated fibrous tissue proliferation. MCH ($AUC = 0.7456$), HCT and MCV, as the core indirect indicators of nutritional status, were related to the absorption and utilization of haematopoietic nutrients (Iron, Vitamin B12, Folate), which further supported the association between nutritional deficiency and the progression of intestinal fibrosis in Crohn's disease patients. Absolute LYM ($AUC = 0.7266$) and HGB ($AUC = 0.7074$) reflect immune status and anemia severity, respectively. A lower LYM count may indicate inflammation-related immunosuppression, whereas reduced HGB reflects the chronic, debilitating effects of the disease. Together, they can serve as supplementary markers of disease progression.

Based on the eight high-performance indicators identified through ROC curve analysis, we further compared indicator levels between the two groups. As shown in Table 1, all eight laboratory indicators differed significantly between the groups (all $P < 0.0001$).

Compared with the control group, patients with Crohn's disease-related intestinal fibrosis had significantly higher APTT levels, while GLU, PDW, MCV, HCT, MCH, LYM, and HGB levels were significantly lower (Table 2). These findings suggest that the markers may be associated with the development and progression of intestinal fibrosis in Crohn's disease and may therefore be included in subsequent multivariate analyses.

Table 1: ROC parameters for 35 laboratory markers of intestinal fibrosis in Crohn's disease

Laboratory Parameter	AUC	P value	Laboratory Parameter	AUC	P value
GLU	0.7683	<0.0001	MCHC	0.6099	<0.0001
MCV	0.7651	<0.0001	PO4	0.5967	<0.0001
HCT	0.7590	<0.0001	CL	0.5948	<0.0001
PDW-SD	0.7551	<0.0001	K+	0.5873	<0.0001
APTT	0.7490	<0.0001	MONO	0.5712	<0.0001
MCH	0.7456	<0.0001	EOSR	0.5689	<0.0001
LYM	0.7266	<0.0001	BASO	0.5603	<0.0001
HGB	0.7074	<0.0001	WBC	0.5592	<0.0001
LYMR	0.6896	<0.0001	DD	0.5573	<0.0001
INR	0.6876	<0.0001	EOS	0.5456	<0.0001
RDW-CV%	0.6806	<0.0001	RBC	0.5418	<0.0001
PT	0.6767	<0.0001	FIB	0.5414	<0.0001
Ca ²⁺	0.6681	<0.0001	BASOR	0.5369	<0.0001
MONOR	0.6626	<0.0001	RDW-SD	0.5302	<0.0001
TT	0.6525	<0.0001	Na+	0.5294	<0.0001
PCT	0.6519	<0.0001	MPV	0.5143	<0.0001
PLT	0.6383	<0.0001	NEU	0.5095	<0.0001
NEUR	0.6136	<0.0001			

Table 2: Comparison of 8 high-performance laboratory indicators between the two groups

Laboratory Parameter	Control Group (n=104)	Case group (n = 280)	P value	Direction of change (case vs. control)
GLU	5.21 (4.68-6.29)	4.39 (4.07-4.89)	<0.0001	↓
APTT	28.06 (26.66-29.64)	31.04 (28.79-33.28)	<0.0001	↑
PDW-SD	16.1 (15.9-16.3)	15.6 (13.0-16.0)	<0.0001	↓
MCV	91.1 (88.72-94.12)	85.8 (79.88-89.7)	<0.0001	↓
HCT	40.9 (38.2-44.3)	38.1 (34.2-41.12)	<0.0001	↓
MCH	29.9 (28.7-30.9)	27.85 (25.38-29.42)	<0.0001	↓
LYM	1.84 (1.44-2.25)	1.31 (0.92-1.71)	<0.0001	↓
HGB	135.0 (125.0-145.25)	122.0 (107.0-136.0)	<0.0001	↓

The remaining 27 laboratory markers failed to meet the prespecified screening thresholds, with AUCs ranging from 0.5095 to 0.6896. Because their diagnostic performance was limited and their clinical utility insufficient, they were excluded from the subsequent core analysis. To visually illustrate the differences among the 8 high-performance indicators, a comparative ROC curve analysis figure was created. In the figure, the black straight line represents the reference line (AUC = 0.5), while solid lines of different colors represent the ROC curves of the 8 indicators, reflecting the differences in diagnostic performance among them (Figure 1).

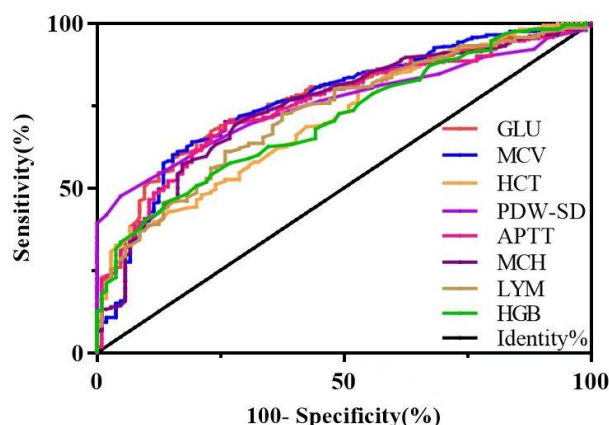


Figure 1: Comparison of ROC Curves for 8 High-Sensitivity Laboratory Markers of Intestinal Fibrosis in Crohn's Disease

Screening and Performance Evaluation of Multi-indicator Combined Prediction Models

Based on the 8 high-performance indicators screened in the previous section, AUC values ranged from 0.7074 to 0.7683, none of which reached the higher diagnostic threshold of 0.80. This indicates that although each individual marker was statistically significant ($P < 0.0001$), its diagnostic performance was limited when used alone, making it difficult to meet the clinical need for accurate identification of intestinal fibrosis. To further improve diagnostic performance, a binary logistic regression model was employed to develop combined predictive models using different combinations of markers, and the diagnostic performance of each model was evaluated by ROC curve analysis. The top 5 combinations by diagnostic performance and their AUC ranges are shown in **Table 3**, and a comparison of the ROC curves with the highest AUC for each combination type is presented in Figure 2-1. The model with the optimal diagnostic performance was selected to provide a noninvasive solution for the early and accurate prediction of intestinal fibrosis in Crohn's disease.

Screening of Multi-indicator Combined Prediction Models

This study constructed all possible combinations of the 8 high-performance indicators and established combined prediction models using 2 to 8 indicators each. Specifically, there were 28 two-indicator models, 57 three-indicator models, 54 four-indicator models, 50 five-indicator models, 28 six-indicator models, 8 seven-indicator models, and 1 eight-indicator model, for a total of 226 combined prediction models. For each combination, a binary logistic regression model was fitted to calculate regression coefficients and prediction probabilities. The prediction probabilities were imported into GraphPad Prism 6.07, and ROC curves were plotted with the false positive rate (1-specificity) on the x-axis and sensitivity on the y-axis. The AUC was calculated using the software's built-in algorithm to quantify the diagnostic performance of the models. Due to the large number of combinations, only the top 5 models ranked by AUC are presented in **Table 3**. The AUC range for each combination model is also recorded. Differences in AUC among the combination models were statistically significant ($P < 0.0001$).

Table 3: Diagnostic performance of different combination models of high-sensitivity laboratory markers for intestinal fibrosis in Crohn's disease

Combination Types	Top 5 Optimal Marker Combinations	AUC	Range of AUC values	P
2-marker combination model	1.PDW-SD+LYM	0.8469	0.8469-0.7090	< 0.0001
	2.MCV+RDW-SD	0.8355		
	3.PDW-SD+MCH	0.8310		
	4.PDW-SD+APTT	0.8282		
	5.APTT+LYM	0.8174		
3-marker combination model	1.GLU+PDW-SD+LYM	0.8855	0.8855-0.7700	< 0.0001
	2.PDW-SD+APTT+LYM	0.8789		
	3.GLU+MCV+PDW-SD	0.8708		
	4.MCV+PDW-SD+LYM	0.8704		
	5.PDWSD+MCH+LYM	0.8689		
4-marker combination model	1.GLU+PDW-SD+APTT+LYM	0.9062	0.9062-0.8247	< 0.0001
	2.GLU+MCV+PDW-SD+LYM	0.8980		
	3.GLU+PDW-SD+MCH+LYM	0.8978		
	4.MCV+PDW-SD+APTT+LYM	0.8947		
	5.GLU+HCT+PDW-SD+LYM	0.8941		
5-marker combination model	1.GLU+MCV+PDW-SD+APTT+LYM	0.9169	0.9169-0.8487	< 0.0001
	2.GLU+PDW-SD+APTT+MCH+LYM	0.9137		
	3.GLU+HCT+PDW-SD+APTT+LYM	0.9088		
	4.GLU+PDW-SD+APTT+LYM+HGB	0.9070		
	5.MCV+PDW-SD+APTT+LYM+HGB	0.8960		
6-marker combination model	1.GLU+MCV+HCT+APTT+LYM+PDW-SD	0.9174	0.9174-0.8621	< 0.0001
	2.GLU+MCV+APTT+MCH+LYM+PDW-SD	0.9170		
	3.GLU+MCV+APTT+LYM+HGB+PDW-SD	0.9161		
	4.GLU+HCT+APTT+MCH+LYM+PDW-SD	0.9152		
	5.GLU+APTT+MCH+LYM+HGB+PDW-SD	0.9138		
7-marker combination model	1.GLU+HCT+APTT+MCH+LYM+HGB+ PDW-SD	0.9190	0.9190-0.8866	< 0.0001
	2.GLU+MCV+HCT+APTT+LYM+HGB+ PDW-SD	0.9180		
	3.GLU+MCV+HCT+APTT+MCH+LYM+ PDW-SD	0.9178		
	4.GLU+MCV+APTT+MCH+LYM+HGB+ PDW-SD	0.9162		
	5.GLU+MCV+HCT+MCH+LYM+HGB+ PDW-SD	0.9075		
8-marker combination model	1.GLU+HCT+APTT+MCH+LYM+HGB+PDW-SD+MCV	0.9197		< 0.0001

Note: The table shows only the top five Optimal Marker Combinations with the highest AUC values for each combination; other combinations with lower values are not listed. The AUC value ranges for combinations of 2-8 markers represent the numerical ranges of all combinations within the corresponding categories.

Performance Evaluation and Analysis of Multi-indicator Combined Models

The diagnostic performance of all indicator combinations was statistically significant ($P < 0.0001$). For 2-marker combinations, the AUC range was 0.7090-0.8469, and the top 5 models ranged from 0.8174 to 0.8469, with the PDW + LYM combination showing the best

performance (AUC = 0.8469). Although this AUC was higher than that of any single marker, using only two markers cannot comprehensively reflect the multidimensional pathophysiological changes involved in intestinal fibrosis (including inflammation, immunity, coagulation, and nutritional metabolism), resulting in substantial diagnostic limitations.

The AUC of the combined diagnosis using 3 to 5 indicators increased gradually, ranging from 0.7700 to 0.8855 (3-indicator combinations: 0.8247-0.9062; 4-indicator combinations: 0.8487-0.9169). The optimal 3-marker model, which consists of GLU + PDW + LYM, achieved an AUC of 0.8855, which was 0.0386 higher than that of the best 2-marker model. The inclusion of GLU in the model indicates that abnormal glucose metabolism may be one of the pathogenic factors of intestinal fibrosis. Among all 4-marker combinations, GLU + PDW + APTT + LYM delivered the best predictive performance with an AUC of 0.9062, which exceeded the 0.90 performance threshold. The optimal 5-indicator model, GLU + MCV + PDW + APTT + LYM, reached an AUC of 0.9169, with MCV introducing additional anemia-related pathological information. Overall, the predictive performance of the combined model improved as more pathological features were incorporated, as the model progressively captures pathological information from multiple aspects of the underlying pathological process, including GLU, APTT, PDW, LYM and MCV.

The model performance remained relatively stable across all combinations of 6 to 8 biomarkers, with consistent AUC values. The AUC of the 6-biomarker model ranged from 0.8621 to 0.9174, while the AUC of the 7-biomarker model ranged from 0.8866 to 0.9190. One 8-biomarker combination achieved an AUC of 0.9197, the highest value among all tested combinations. AUC values varied among the top 5 performing models. For 6-biomarker combinations, the coefficient of variation ranged from 0.9138 to 0.9174, while for 7-biomarker combinations, the coefficient of variation ranged from 0.9075 to 0.9190. The optimal 6-biomarker model was GLU + MCV + HCT + APTT + LYM + PDW, with an AUC of 0.9174. The optimal 7-biomarker model was GLU + HCT + APTT + MCH + LYM + HGB + PDW, with an AUC of 0.9190. The 8-biomarker combination of GLU + HCT + APTT + MCH + LYM + HGB + PDW + MCV obtained the highest AUC of 0.9197. By integrating signals from four pathological dimensions, the model captures associations with metabolic disorders, nutritional deficiencies, coagulation activation, and immunosuppression, thus achieving improved predictive performance. **Figure 2** plots the ROC curves to demonstrate the performance differences across the 8 high-performance biomarkers.

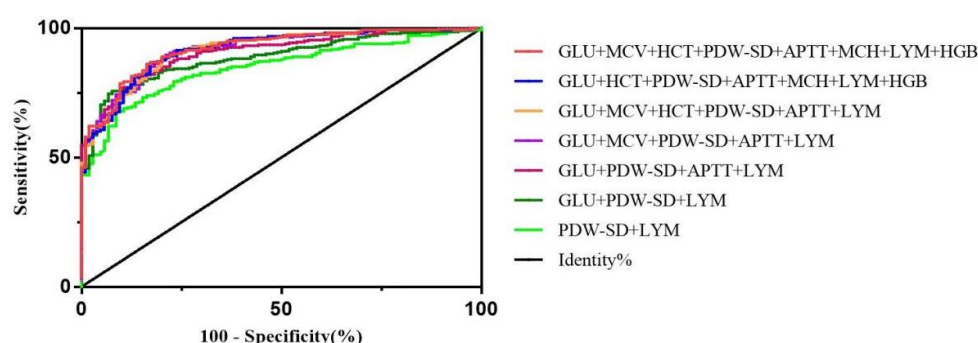


Figure 2: Comparison of the diagnostic performance of the best ROC curves for different combinations of high-value laboratory markers of intestinal fibrosis in Crohn's disease

DISCUSSION

This study investigated the noninvasive prediction of intestinal fibrosis in Crohn's disease. In a retrospective analysis of clinical and laboratory data from 384 participants, 8 high-performance laboratory indicators (GLU, MCV, HCT, PDW, APTT, MCH, LYM, and HGB) were identified. A high-performance model was then developed using combinations of these indicators, and the predictive performance of different combinations was validated. As shown in the previous section, GLU performed best among single markers (AUC = 0.7683); however, multi-marker models performed better than single markers. The optimal performance of the various marker combinations was as follows: the 2-marker model (AUC = 0.8469), the 3-marker model (AUC = 0.8855), the 4-marker model (AUC = 0.9062), the 5-marker model (AUC = 0.9169), the 6-marker model (AUC = 0.9174), the 7-marker model (AUC = 0.9190), and the 8-marker model (AUC = 0.9197). When the number of markers exceeded four, the AUC exceeded 0.90, and the inclusion of additional valid markers was associated with improved diagnostic performance.

Intestinal fibrosis in Crohn's disease is a complex pathological process mediated by chronic inflammation and involves multiple core pathological dimensions. GLU, the single marker with the best predictive performance, may be associated with intestinal fibrosis in Crohn's disease. Chronic metabolic disorders combined with inflammation may accelerate myofibroblast proliferation, leading to fibrosis and strictures. This is consistent with findings reported by Fan et al. ^[11], who found that the TyG index is significantly positively correlated with the risk of Crohn's disease and that high TyG index levels significantly increase the risk of IBD and its subtypes.

HCT, MCH, HGB, and MCV are all nutrition-related red blood cell indicators. Long-term damage to the intestinal mucosa in patients with Crohn's disease leads to impaired absorption of iron and folate, which in turn causes anemia and malnutrition. Nutritional deficiencies and related anemia are therefore common among patients with IBD, manifesting as abnormalities in MCV, MCH, and HGB. These findings are consistent with several previous studies ^[12-14]. Among platelet parameters, PDW, when combined with other laboratory markers, can improve the diagnostic accuracy for Crohn's disease. This differs from the conclusions of Xu et al. ^[15], who found that although abnormalities in platelet parameters are closely associated with IBD, there was no statistically significant overall difference in PDW between the IBD group and healthy controls. In contrast, Galijašević et al. reported that PDW was associated with distinguishing active from remitting phases of Crohn's disease, although its performance was moderate (AUC = 0.789) ^[16].

Prolonged APTT may be associated with deep intestinal inflammation and fibrosis and increases as disease activity worsens. This finding differs from that reported by Zhang et al. ^[17], who found a significant difference in APTT between patients with Crohn's disease and healthy controls but no difference before and after disease progression. Low LYM levels are negatively correlated with Crohn's disease prevalence ^[18]. LYM serves as a valuable, low-cost adjunctive diagnostic marker; when combined with other laboratory markers and imaging studies, it can improve the prediction of intestinal fibrosis in Crohn's disease.

Each indicator reflects a distinct pathological feature. Combining multiple indicators into a single model may improve predictive performance, overcome the limitations of individual indicators, and enable early, noninvasive prediction of intestinal fibrosis in Crohn's disease.

The results showed that the multi-marker model outperformed models based on a single marker. The pathogenesis of intestinal fibrosis in Crohn's disease involves multiple interacting factors, including metabolic, immunological, and genetic processes. Because no single marker can reflect the cumulative effects of various nutrient deficiencies or reliably distinguish among Crohn's disease -related complications, single-marker approaches have inherent limitations. Combining markers from different dimensions, such as inflammation, nutrition, and coagulation, can therefore improve diagnostic performance ^[19,20]. In this study, the model incorporating eight laboratory markers achieved better diagnostic performance, as the distinct pathological factors represented by these markers complemented one another across multiple dimensions.

The optimal 4-marker model achieved an AUC of 0.9062, exceeding the threshold of $AUC > 0.90$; the inclusion of APTT suggests that the functional status of the coagulation system also plays a role in the fibrosis process. With five markers combined, the optimal model achieved an AUC of 0.9169, representing an increase of 0.0107 over the four-marker model. The newly added marker was MCV. Including red blood cell parameters may reflect disease-related malabsorption and chronic anemia. Among the six-marker combinations, the optimal model-GLU + MCV + HCT + APTT + LYM + PDW—achieved an AUC of 0.9174, an increase of just 0.0005 over the five-marker model. For seven-marker combinations, the best model-GLU + HCT + APTT + MCH + LYM + HGB + PDW—had an AUC of 0.9190, improving by 0.0016 over the six-marker model. The eight-marker combination reached a maximum AUC of 0.9197, only 0.0007 higher than that of the seven-marker model. Overall, the cumulative increase in AUC from five to eight markers was just 0.0028 (0.9169 → 0.9197). The newly added parameters-HCT, HGB, and MCH—are all red blood cell indices and may introduce multicollinearity. This finding is consistent with the conclusions reported by Poulsen et al. on serum markers of collagen remodeling: that study also found that although a single collagen marker could distinguish between stenotic and luminal-type Crohn's disease, the combination of PRO-C6, PRO-C3, and PRO-C5 achieved the highest AUC of 0.910, and adding further markers did not substantially improve performance ^[21]. Although the 8-marker model achieved the highest AUC, it included several functionally similar red blood cell parameters (HCT, HGB, and MCH) that may introduce multicollinearity. The 5-marker model (GLU + MCV + PDW + APTT + LYM) was therefore ultimately recommended, as it covers multiple factors—including metabolic abnormalities, immune dysregulation, inflammatory activation, and coagulation abnormalities—while achieving comparable diagnostic performance with a more parsimonious marker combination. Therefore, combined analysis of multiple laboratory markers representing different pathophysiological processes is important for effectively distinguishing fibrotic stenosis from inflammatory stenosis. Similarly, a previous study ^[22] pointed out that when constructing predictive models, including markers with highly similar functions makes it difficult to improve the model's discriminatory power and can confuse the interpretation of results due to issues such as multicollinearity, increasing model complexity and uncertainty. The 5 composite markers identified in this study are all routine clinical tests that are easily accessible, inexpensive, and widely applicable. They are suitable not only for the assessment of intestinal fibrosis in Crohn's disease and preoperative risk stratification in hospitals but can also, after appropriate simplification, be adapted for preliminary screening in primary care settings. Their flexible application within a tiered healthcare system demonstrates advantages in both predictive performance and clinical utility.

Future research could focus on the following three areas: (1) multicenter studies with clinically heterogeneous populations should be promoted to validate the model, comprehensively assess its clinical applicability across different geographic regions and levels of medical care, and facilitate large-scale clinical implementation; (2) iterative model optimization using classical machine learning algorithms such as random forests and logistic regression should be implemented, with indicator weights recalibrated and model parameters fine-tuned using clinical data from a larger sample to improve overall predictive performance; (3) the value of combined testing of the marker combination identified in this study with novel molecular biomarkers related to fibrosis—such as microRNAs (miRNAs) and fecal calprotectin—should be further explored to provide a more comprehensive basis for early intervention, clinical risk stratification, and the optimization of personalized treatment plans for intestinal fibrosis in Crohn's disease within the context of precision medicine.

CONCLUSION

This study enrolled 384 participants and ultimately identified 8 high-performance predictive markers for intestinal fibrosis in Crohn's disease (all $P < 0.0001$, $AUC > 0.70$), covering four major pathological dimensions: metabolism, nutrition, coagulation, and immunity. Among single markers, GLU demonstrated the best predictive performance ($AUC = 0.7683$). In comparison, multi-marker combination models outperformed any single marker. Among the 226 combinations, the best-performing model for each combination size (2-8 markers) was selected, resulting in 7 optimal models. The 8-marker model (GLU + HCT + APTT + MCH + LYM + HGB + PDW + MCV) achieved an AUC of 0.9197, while the 5-marker model (GLU + MCV + PDW + APTT + LYM) achieved an AUC of 0.9169. Overall, the 5-marker model provided a strong balance of accuracy and clinical utility. All five markers are measured by routine laboratory tests that are noninvasive, low-cost, and do not require specialized platforms, making the model suitable for initial screening and routine clinical use. However, additional data are needed to confirm its clinical value. Future multicenter studies should further evaluate the model's applicability, and machine learning algorithms may help optimize the weights assigned to each marker. Further research will also examine how to combine this model with novel molecular biomarkers, including fibrosis-related markers, to improve prediction accuracy and support individualized diagnosis and treatment.

Author's Contributions

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All the authors have read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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