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Study on the predictive model of response of patients with inflammatory bowel disease to infliximab treatment.

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Keywords: Inflammatory Bowel Diseases; Infliximab; Drug Therapy; Response; Disease forecasting models.

Abstract. This study aimed to develop a predictive model for how patients with inflammatory bowel disease (IBD) respond to infliximab (IFX) treatment. One hundred adult IBD patients admitted to Shulan (Hangzhou) Hospital from August 2023 to November 2024 were included and divided into response and non-response groups based on their reaction to IFX. The response group consisted of 57 patients (57.0%), while the non-response group had 43 patients (43.0%). Clinical data, including gender, age, BMI, disease type (Crohn's disease/ulcerative colitis), disease activity indices (CDAI/UCAI), history of IFX treatment, and infusion reactions, were collected and compared between the two groups. Additionally, biomarker levels, such as TNF-α, CRP, calprotectin, anti-infliximab antibody (ATI), IL-6, and IL-8, were measured during the midcourse of IFX treatment. Single-factor analysis identified variables that differed, and logistic regression showed that calprotectin level (OR=1.099, 95%CI=1.039-1.163), ATI (OR=3.756, 95%CI=1.222-11.546), IL-6 (OR=1.261, 95%CI=1.069-1.488), and IL-8 (OR=1.014, 95%CI=1.004-1.024) were key factors influencing treatment response ($p < 0.05$). A nomogram was created using these factors to predict treatment response in IBD patients. ROC analysis showed AUC values of 0.809, 0.762, 0.850, and 0.775 for calprotectin, ATI, IL-6, and IL-8, respectively, with corresponding 95% confidence intervals. The calibration curve indicated good model fit. These findings underscore the important roles of these cytokines in IBD pathogenesis and the action of IFX, as well as the high predictive power of the nomogram model.

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Estudio sobre el modelo predictivo de la respuesta de los pacientes con enfermedad inflamatoria intestinal al tratamiento con infliximab.

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Palabras clave: Enfermedades Inflamatorias del Intestino; Infliximab; Tratamiento Farmacológico; Respuesta; Modelos de predicción de enfermedades.

Resumen. Este estudio tuvo como objetivo desarrollar un modelo predictivo de la respuesta de los pacientes con enfermedad inflamatoria intestinal (EII) al tratamiento con infliximab (IFX). Se incluyeron un total de 100 pacientes adultos con EII ingresados en el Hospital Shulan (Hangzhou) desde agosto de 2023 hasta noviembre de 2024, y se dividieron en grupos de respuesta y no respuesta según su reacción al IFX. El grupo de respuesta tenía 57 pacientes (57,0%), mientras que el de no respuesta, 43 (43,0%). Se recolectaron y compararon datos clínicos, como género, edad, IMC, tipo de enfermedad (Crohn/colitis ulcerosa), índices de actividad de la enfermedad (CDAI/UCAI), historial de tratamiento con IFX y reacciones a la infusión, entre ambos grupos. Además, se midieron los niveles de biomarcadores, incluidos TNF-α, PCR, calprotectina, ATI, IL-6 e IL-8, durante el período intermedio del tratamiento con IFX. El análisis de variables individuales identificó diferencias significativas, y el análisis de regresión logística reveló que los niveles de calprotectina (OR=1,099, IC95%=1,039-1,163), ATI (OR=3,756, IC95%=1,222-11,546), IL-6 (OR=1,261, IC95%=1,069-1,488) e IL-8 (OR=1,014, IC95%=1,004-1,024) eran factores clave que influyen en la respuesta al tratamiento ($p<0,05$). Se construyó un nomograma basado en estos factores para predecir la respuesta al tratamiento en pacientes con EII. El análisis de la curva ROC mostró valores de AUC de 0,809, 0,762, 0,850 y 0,775 para calprotectina, ATI, IL-6 e IL-8, respectivamente, con los rangos del IC del 95% correspondientes. La curva de calibración indicó un buen ajuste del modelo. Estos hallazgos destacan el papel importante de estas citocinas en la patogénesis de la EII y en el mecanismo terapéutico del IFX, así como el alto valor predictivo del nomograma.

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INTRODUCTION

Inflammatory Bowel Disease (IBD) is a complex, chronic gastrointestinal inflammatory condition that mainly includes Crohn's disease and ulcerative colitis. Its pathogenesis has not been fully understood yet [1]. Globally, the incidence and prevalence of IBD are continuously rising, especially in Western developed countries. However, in recent years, its incidence has also sharply increased in newly industrialized regions like Asia [2]. IBD causes long-term pain and suffering for patients, seriously affecting their quality of life, and also places a significant economic burden on the healthcare system [3].

The approach to treating IBD has shifted greatly from traditional medications to biological therapies. During the era of conventional treatments, 5-aminosalicylic acid drugs, corticosteroids, and immunosuppressants were the primary options for managing IBD. However, these medications often faced challenges such as limited effectiveness and notable side effects, making it difficult to fully meet clinical needs [4, 5]. With a deeper understanding of IBD's causes, especially the development of targeted therapies aimed at inflammatory mediators like tumor necrosis factor (TNF), there has been groundbreaking progress in IBD treatment. Infliximab (IFX), the first TNF-α inhibitor approved for treating IBD, effectively reduces intestinal inflammation and significantly improves patients' symptoms and quality of life by specifically binding to and neutralizing TNF-α [6, 7]. The successful use of infliximab not only offers new treatment options for IBD patients but also encourages widespread use and ongoing research of biological agents in managing IBD.

Although IFX has shown a remarkable curative effect in the treatment of IBD, there are significant individual differences in patients' treatment response. Some patients responded well to IFX, achieving rapid symptom relief and a significant reduction in disease activity. However, some patients exhibit poor responses and even primary or secondary treatment failure. The heterogeneity of this therapeutic response is a key problem that urgently requires resolution in the treatment of IBD [8].

Heterogeneity in treatment response not only affects patients' clinical prognosis but also increases medical costs and psychological burden. For patients with poor response, it may be necessary to try other biological agents or immunosuppressants, which not only increase treatment costs but may also bring additional drug-related side effects and risks [9,10]. In addition, heterogeneity in treatment response poses challenges for physicians in developing treatment plans. Doctors need to provide patients with personalized treatment programs, given limited medical resources, to achieve optimal treatment outcomes.

To optimize treatment strategies for IBD patients and improve IFX efficacy, researchers have begun exploring factors that affect treatment response. These factors include, but are not limited to, the patient's age, sex, disease type, disease activity, previous treatment history, complications, serological marker levels, and genetic background[11,12]. However, given the complexity of IBD pathogenesis and interpatient variability, it is often difficult for a single factor to fully account for the heterogeneity of treatment responses. Therefore, it has become a challenging and forward-looking research direction to develop a predictive model that comprehensively considers multiple factors and individually predicts the treatment response of IBD patients to IFX [13,14].

A prediction model is a mathematical system based on large datasets that generates predictions for specific events or outcomes by analyzing and processing input data. In medicine, predictive models are widely used in areas including disease diagnosis, prognosis assessment, treatment strategy selection, and others [15,16]. In the treatment of IBD, the potential of prediction models also remains broad [17, 18].

First, the prediction model can help physicians more accurately evaluate IBD patients' responses to infliximab, enabling more personalized treatment plans. Using the model, doctors can identify patients unlikely to respond to infliximab in advance and adjust treatment strategies accordingly to avoid unnecessary drug use and waste of medical resources [19]. Additionally, the model can suggest other potentially effective treatments or strategies tailored to individual patient conditions, thereby improving overall treatment outcomes. Second, the prediction model can also offer more comprehensive health management services for patients with IBD. By regularly monitoring relevant

indicators and dynamically evaluating them with the model, healthcare providers can detect changes in patients' conditions promptly and implement appropriate interventions, effectively preventing disease recurrence and complications. This approach not only enhances patients' quality of life but also helps reduce medical costs and social burdens [20, 21]. Finally, research on the prediction model can also advance understanding of IBD's pathogenesis and treatment strategies. By analyzing the key factors identified by the model, researchers can further uncover the molecular mechanisms and immune regulatory networks involved in IBD, providing a theoretical basis and experimental evidence for the development of new drugs and therapies [22]. This will promote continuous innovation and progress in IBD treatment.

Given the variability in IBD patients' responses to infliximab and the wide-ranging applications and challenges of predictive models in IBD treatment, this study aims to develop a predictive model for infliximab response in IBD patients through retrospective analysis. It will utilize existing medical resources, gather comprehensive patient data, and apply scientific methods to clean and standardize the data, build an accurate and reliable prediction model, and rigorously validate and evaluate it. The importance of this study lies in: providing more personalized treatment plans for IBD patients, enhancing treatment efficiency and success rates, reducing medical costs and patient burden, and equipping doctors with more precise tools for disease management and prediction. This enables timely detection of changes in patients' conditions and the implementation of appropriate interventions to improve overall treatment outcomes and quality of life. Additionally, it promotes an in-depth understanding of IBD pathogenesis and treatment strategies, offers a theoretical basis and experimental evidence for developing new therapies, and supports continuous innovation and advancement in IBD treatment.

PATIENTS AND METHODS

One hundred adult patients with IBD admitted to Shulan (Hangzhou) Hospital, Shulan International Medical College, Zhejiang Shuren University, from August 2023 to November 2024 were included.

Inclusion criteria

- Inflammatory bowel disease (IBD) was diagnosed by professional doctors through endoscopy and imaging findings.
- No recent (within six months) treatment with other biological agents or immunosuppressants.
- 20~65 years old.
- Patients treated with infliximab for a certain period (more than 14 weeks).
- The patient and his family agreed and signed the informed consent form.

Exclusion criteria

- Clinical data were incomplete.
- Have a clear history of infection in the respiratory system or urinary system recently.
- Taking aspirin and other anticoagulants recently.
- Complicated with serious diseases such as heart, liver, kidney, biliary system, and hematopoietic system.
- Combined with autoimmune diseases.
- Have a history of trauma and operation during pregnancy and within three months.
- Previous history of biological treatment.

METHOD

Baseline data collection

Baseline data of all IBD patients were collected before the initiation of infliximab

(IFX) treatment, including gender, age, BMI index, disease type [Crohn's disease (CD) or ulcerative colitis (UC)], baseline disease activity [Crohn's disease activity index (CDAI) [23] and ulcerative colitis activity index (UCAI) [24]], prior IFX treatment history, and the occurrence of infusion-related reactions (e.g., chest tightness or chest pain) during previous treatments. In addition, baseline biomarkers—such as serum levels of tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), anti-Infliximab antibody (ATI), interleukin-6 (IL-6), interleukin-8 (IL-8), and fecal calprotectin—were measured prior to treatment initiation to assess their predictive value for treatment response.

Assessment instrument

The CDAI score consists of many factors, including symptoms (such as abdominal pain, diarrhea, weight loss, etc.), signs (such as abdominal mass, perforation, intestinal obstruction, etc.), laboratory indicators (such as hemoglobin level and white blood cell count) and complications (such as peripheral arthritis, skin lesions, etc.). The score ranges from 0 to 600, and higher scores indicate more severe disease. Specific scoring criteria: remission period: < 150 points; mild activity period: 150~220 points; moderate activity period: 221~450 points; severe activity period: > 450 points.

The UCAI score is primarily based on patients' clinical manifestations, including defecation frequency, presence of blood in stool, endoscopic findings, and physicians' overall assessment. For example, the improved Mayo scoring system is a common form of UCAI, and its scoring comprises four components: daily defecation frequency, presence of blood in stool, degree of mucosal injury under endoscopic examination, and overall physician assessment. The scoring range is usually 0~12 points. Specific grading: remission period: UCAI score < 2; mild activity period: 2~3 points; moderate activity period: 4~6 points; severe activity period: > 6 points.

Biochemical index detection method

Four mL of fasting venous blood was routinely collected and placed in a disposable vacuum blood collection tube without anticoagulant for later use. The ELISA method (the kits were purchased from Beijing Baiao Innovation Technology Co., Ltd., Beijing Suolaibao Technology Co., Ltd., Aimeijie Technology Co., Ltd., Jianglai Biology and Wuhan Feien Biotechnology Co., Ltd. in turn; the serial numbers/goods numbers are (E-EL-H0109c, SEKH-0138, KA4933, JL14113, QT-EH0205) was used to detect serum tumor necrosis factor -α (TNF-α), C-reactive protein (CRP), anti-infliximab antibody (ATI), and interleukins (IL).

An ELISA kit (article number HR0593; purchased from Suzhou Herui Pharmaceutical Technology Co., Ltd.) was used to measure calprotectin levels in the supernatant of routinely collected fecal samples from patients.

The above indicators are included in the baseline data.

Response vs. Non-response evaluation standard

Based on post-IFX treatment responses, patients were classified into a response group and a non-response group.

Response group: After treatment, clinical symptoms such as diarrhea, abdominal pain, bloody stool, and intestinal absorption disorder resolved or improved significantly, and no new complications, including oral ulcer, gallstone, arthritis, and gastrointestinal bleeding, occurred. Colonoscopy showed that intestinal mucosal inflammation, including congestion, edema, erosion, and ulceration, was significantly reduced or absent. Intestinal mucosal healing is good, as evidenced by reduced ulcer size, increased mucosal smoothness, and reduced submucosal edema. The intestinal stenosis or dilatation has improved, and intestinal patency has increased.

Unresponsive group: there was no significant change or aggravation of clinical symptoms after treatment; symptoms such

as diarrhea, abdominal pain, and others persisted or worsened. New complications may have occurred, or the original complications may have been aggravated. Colonoscopy showed that there was no significant change or aggravation of intestinal mucosal inflammation, such as the expansion of the lesion scope and the increase in ulcer depth. Intestinal stenosis or dilatation has not been improved or aggravated.

Ethical considerations

This study strictly adheres to the principles of the Declaration of Helsinki, and all research procedures comply with international ethical standards. Strictly adheres to ethical principles to ensure the rationality of the research design, the compliance with data use, and the full protection of participants' privacy. The research should aim to improve treatment effectiveness, respect the rights and interests of all participants, avoid bias, and ensure the fairness and transparency of the research results.

Statistical methods

SPSS 22.0 was used for statistical analysis. Measurement data that conformed to the normal distribution were presented as (S), t-test; count data were presented as n (%), χ^2-test; and Logistic regression was used for correlation factor analysis. The nomogram model was constructed in R, and the Bootstrap method was used for internal validation. A calibration curve and receiver operating characteristic (ROC) curve were drawn to evaluate the nomogram model. Inspection standard $\alpha=0.05$.

RESULTS

Immune response

A total of 57 cases, accounting for 57.0% of all IBD patients, were included in the response group. The remaining 43 patients were unresponsive (43.0%) and were included in the non-response group.

Baseline data analysis

In the baseline data of the two groups, the levels of TNF-α, CRP, calprotectin, ATI, IL-6, IL-8, and other cytokines were lower than those of the non-response group. There was no significant difference in other data (Table 1).

Logistic regression analysis

The treatment response of patients with IBD was used as the dependent variable (response = 0, non-response = 1). The data with a statistically significant difference in Table 1 were included in the independent variable, and Logistic regression analysis was conducted. The results showed that the levels of calprotectin (*OR*=1.099, 95%*CI*=1.039~1.163), ATI (*OR*=3.756, 95%*CI*=1.222~11.546), IL-6 (OR=1.261, 95%CI=1.069~1.488), and IL-8 (OR=1.014, 95%CI=1.004~1.024) are the key factors affecting the response of patients with IBD after treatment ($p<0.05$) (Table 2).

Construction and verification of the nomogram model

Based on the results of the logistic regression analysis, a nomogram was developed to predict treatment response in IBD patients (Fig. 1). ROC curve analysis showed that the AUC values for calprotectin level, ATI level, IL-6 level, and IL-8 level in this model were 0.809, 0.762, 0.850, and 0.775, with 95% confidence intervals of 0.719–0.881, 0.666–0.841, 0.765–0.913, and 0.681–0.853 (Fig. 2). The calibration curve indicates a good fit for the nomogram model (Fig. 3).

DISCUSSION

Analysis of baseline data difference between response and non-response groups

In this retrospective study, we examined how patients with inflammatory bowel disease (IBD) responded to infliximab (IFX) and developed a predictive model.

Table 1. Comparison of two groups of baseline data.

Index		Group		χ^2/t	p
		Response group (n=57)	Non-response group (n=43)		
Gender [n (%)]	Male	33 (57.89)	28 (65.12)	0.537	0.464
	Female	24 (42.11)	15 (34.88)		
BMI (kg/m^2)		22.07±0.90	21.86±0.63	1.275	0.205
Type of disease [n (%)]	CD	20 (35.09)	17 (39.53)	0.208	0.648
	UC	37 (64.91)	26 (60.47)		
Age (years)	CD	33.24±3.09	34.34±4.86	0.834	0.410
	UC	37.52±5.48	38.48±4.32	0.743	0.460
Disease activity (points)	CDAI	219.25±16.83	222.37±21.65	0.492	0.626
	UCAI	4.89±0.53	5.04±0.66	1.020	0.312
History of IFX treatment [n (%)]	Existent	3 (5.26)	7 (16.28)	3.305	0.069
	Non-existent	54 (94.74)	36 (83.72)		
Infusion reaction [n (%)]	Chest Tightness/ Chest pain	1 (1.75)	1 (2.33)	1.283	0.733
	Dyspnea	0	1 (2.33)		
	Flushing/Urticaria	0	1 (2.33)		
	Generate heat	1 (1.75)	2 (4.65)		
Gastrointestinal reaction [n (%)]	Nausea/Vomiting	3 (5.26)	4 (9.30)	0.774	0.679
	Abdominalgia	0	1 (2.33)		
	Diarrhea/ Constipation	1 (1.75)	1 (2.33)		
TNF-α level (ng/L)		24.65±3.26	26.57±3.81	2.700	0.008
CRP level (mg/L)		7.58±1.21	9.23±1.87	5.329	<0.001
Calprotectin level (μg/g)		105.09±14.68	123.34±14.74	6.146	<0.001
ATI level (ng/mL)		3.17±0.64	3.82±0.74	4.665	<0.001
IL-6 level (pg/mL)		30.04±5.66	37.70±5.32	6.879	<0.001
IL-8 level (pg/mL)		567.48±78.63	662.70±89.59	5.646	<0.001

BMI: Body Mass Index; CD: Crohn's Disease; UC: Ulcerative Colitis; CDAI: Crohn's Disease Activity Index; UCAI: Ulcerative Colitis Activity Index; TNF-α: Tumor Necrosis Factor-α; CRP: C-reactive Protein; ATI: Anti-Infliximab Antibody; IL-6: Interleukin-6; IL-8: Interleukin-8.

Data is expressed as n (%) or mean +- standard deviation. t: independent-samples t-test, χ^2: Chi-square test.

The results showed that 57 patients (57.0%) responded in this study, and these patients were included in the response group. The remaining 43 patients were non-responders (43.0%) and were included in the non-response group. This proportion distribution suggests that although IFX therapy has a certain effect on IBD patients, there are still many patients who can't get the ideal therapeutic effect.

Table 2. Logistic regression analysis of related influencing factors

Correlative factor	β	SE	Wald χ^2	*p*-value	OR	95%*CI*
TNF-α level	0.068	0.107	0.400	0.530	1.070	0.867~1.319
CRP level	0.323	0.272	1.408	0.235	1.381	0.810~2.354
Calprotectin level	0.094	0.029	10.596	0.001	1.099	1.039~1.163
ATI level	1.323	0.573	5.334	0.021	3.756	1.222~11.546
IL-6 level	0.232	0.084	7.622	0.006	1.261	1.069~1.488
IL-8 level	0.014	0.005	7.732	0.008	1.014	1.004~1.024

Note: TNF-α: Tumor Necrosis Factor-α; CRP: C-reactive Protein; ATI: Anti-Infliximab Antibody; IL-6: Interleukin-6; IL-8: Interleukin-8.

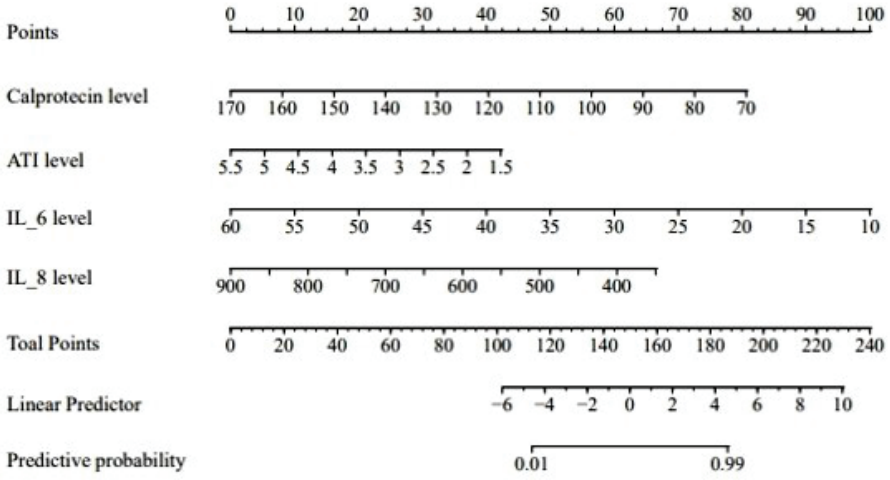

Fig 1. Risk prediction nomogram model.

ATI: Anti-Infliximab Antibody; IL-6: Interleukin-6; IL-8: Interleukin-8.

Risk prediction nomogram model is a visual, point-based tool that translates the final logistic-regression model into a clinician-friendly graphic. It is built on the four independent predictors that remained significant after multivariable adjustment: Calprotectin level, ATI level, IL-6 level, IL-8 level. Locate each biomarker value on its axis, sum the corresponding points, drop the total to the probability scale to read the predicted chance of non-response to infliximab.

Upon further comparison of baseline characteristics between responders and non-responders, this study revealed significant variations in TNF-α, CRP, calprotectin, ATI, IL-6, and IL-8 levels. Specifically, the levels of these cytokines in the response group were lower than those in the non-response group. This discovery provides an important clue and a basis for developing a predictive model in the future.

As IFX's direct target, TNF-α is crucial in IBD development [25]. This study found that, although TNF-α concentrations in both the response and non-response groups exceeded normal levels, they were notably lower in the response group than in the non-response group. This result suggests that TNF-α levels may reflect the intensity of intestinal inflammation and, in turn, influence the therapeutic outcome of IFX. In patients receiving effective IFX treatment, the decrease in TNF-α levels may indicate that IFX neutralizes TNF-α more effectively, thereby reducing intestinal inflammation [26].

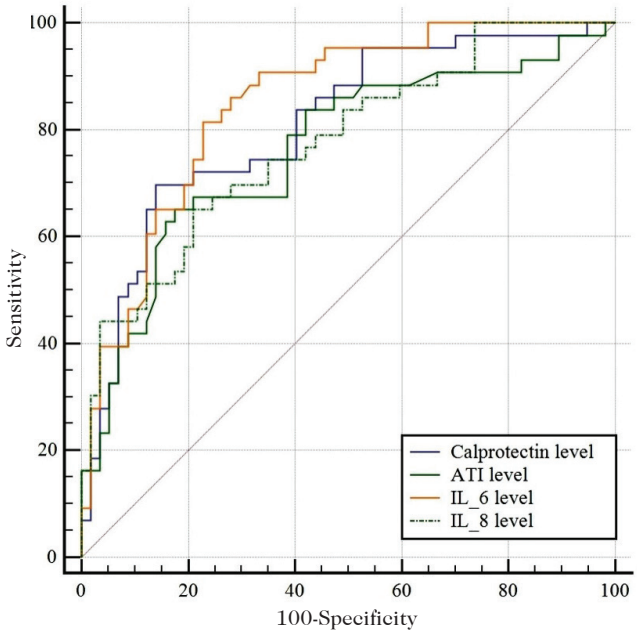

Fig. 2. ROC curve.
ATI: Anti-Infliximab Antibody; IL-6: Interleukin-6; IL-8: Interleukin-8.

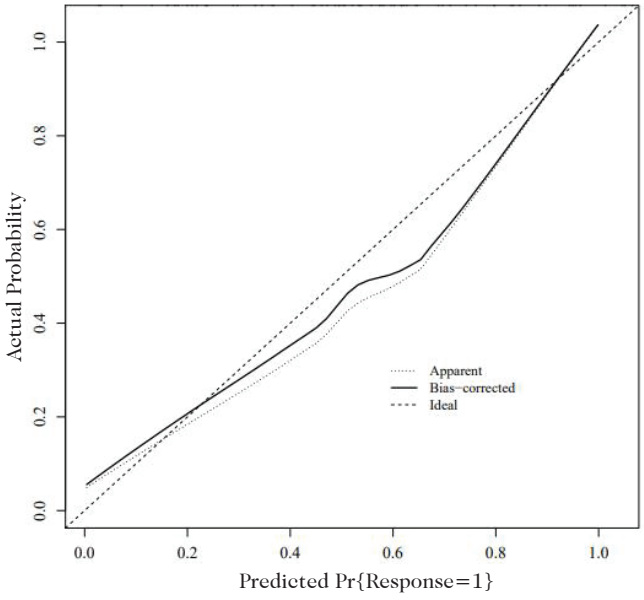

Fig 3. Calibration curve.

CRP serves as a marker of acute inflammation, indicating the body's inflammatory activity level [27]. This study revealed lower CRP levels among responders than among non-responders, consistent with trends in TNF-α levels. A decrease in CRP levels may indicate relief of intestinal inflammation and thus serve as an auxiliary index for predicting the IFX response. However, it is worth noting that CRP levels may be influenced by multiple factors, such as infection and trauma, and therefore should be considered comprehensively in clinical practice.

In addition to the above cytokines, we compared differences in age, sex, disease type, and history between the response and non-response groups. However, this study found no significant difference between the two groups in the baseline data. This result suggests that the treatment response to IFX may be more influenced by the intestinal local inflammatory environment.

Correlation analysis between key cytokines and IFX treatment response

Calprotectin: a sensitive marker of intestinal inflammation and a potential predictor of IFX response.

This study found a notable disparity between response and non-response groups, with Logistic regression analysis confirming calprotectin level as a crucial predictor of IBD patients' response to IFX treatment (OR=1.099, 95%CI=1.039~1.163). This discovery implies that calprotectin is crucial for monitoring IBD inflammation and may serve as a predictive indicator of IFX treatment response.

Calprotectin is a calcium-binding protein primarily secreted by neutrophils, and its elevated expression in the intestine is often closely linked to the severity of the intestinal inflammation [28]. In patients with IBD, an increase in calprotectin levels usually indicates active intestinal inflammation. However, the research revealed that, although calprotectin levels in responders were above normal, they were markedly lower than those of non-responders, potentially because IFX treatment alleviated intestinal inflammation. As an anti-TNF-α monoclonal antibody, IFX can reduce intestinal inflammation by specifically neutralizing TNF-α. Therefore, we speculate that the decrease in calpro-

tectin levels in patients receiving effective IFX may reflect the alleviation of intestinal inflammation and could serve as a sensitive index for predicting the IFX response.

Deeper insights into calprotectin's role in the IFX response suggest its potential involvement in modulating the NF-κB pathway. NF-κB serves as a crucial regulatory protein essential for inflammatory responses. When the intestine is injured or infected, NF-κB is activated, inducing the expression of a series of inflammatory cytokines, including TNF-α, IL-6, and IL-8. The release of calprotectin may affect NF-κB activity through an unknown mechanism, thereby indirectly influencing the expression levels of inflammatory factors [29,30]. In patients receiving effective IFX treatment, a decrease in calprotectin levels may indicate inhibition of the NF-κB signaling pathway, thereby reducing the production of inflammatory mediators and promoting the regression of intestinal inflammation.

ATI: Correlation between Drug Antibody Reaction and Response State of IFX

In this study, the ATI (anti-IFX antibody) level has also been established as a crucial predictor of IBD patients' response to IFX treatment (*OR*=3.756, 95%*CI*=1.222~11.546). This discovery underscores the importance of ATI in the treatment response to IFX and suggests that ATI levels may be a key factor influencing the efficacy of IFX.

In patients, the therapeutic effect of IFX may be influenced by the immune system. When IFX is administered, some patients may develop antibodies (ATI) against IFX, which may bind to IFX, thereby reducing its biological activity and further affecting its therapeutic effect [31]. Therefore, the increase in ATI level often indicates a decrease in the IFX treatment response.

Further analysis of the molecular mechanism of ATI in the IFX response indicates that ATI may influence the pharmacokinetics and pharmacodynamics of IFX. On the one hand, the combination of ATI and IFX may accelerate the clearance of IFX, thereby reducing its concentration in the body and potentially affecting its therapeutic effect. On the other hand, the combination of ATI and IFX may also affect the binding of IFX to TNF-α, thereby reducing the neutralizing activity of IFX [32, 33]. Therefore, in patients receiving effective IFX treatment, a decrease in ATI levels may indicate that IFX maintains high biological activity in vivo, thereby neutralizing TNF-α more effectively and reducing intestinal inflammation.

IL-6 and IL-8: Dual Roles of Inflammatory Factors and Predictive Value of IFX Response

Research revealed IL-6 and IL-8 concentrations as crucial indicators of IBD patients' response to IFX treatment (IL-6: *OR*=1.261, 95%*CI*=1.0691.488; IL-8: *OR*=1.014, 95%*CI*=1.0041.024). This discovery reveals the important roles of IL-6 and IL-8 in the pathogenesis of IBD and in the therapeutic response to IFX.

IL-6 and IL-8 are two key inflammatory cytokines that play a central role in the pathogenesis of IBD. On the one hand, IL-6 and IL-8 can induce inflammatory responses in intestinal mucosal cells and promote the progression of intestinal inflammation. On the other hand, they can also affect the function of the intestinal immune system and further exacerbate the progression of intestinal inflammation [34, 35]. Therefore, the increase of IL-6 and IL-8 levels often indicates the aggravation of IBD patients.

However, this study found that although IL-6 and IL-8 levels in the response group were higher than normal, they were markedly lower than in the non-response group. This result suggests that the decrease in IL-6 and IL-8 levels may reflect the relief of intestinal inflammation in patients with effective IFX treatment. Further analysis of the molecular mechanisms of IL-6 and IL-8 in the IFX response indicates that they may regulate multiple signaling pathways, including the JAK-STAT, NF-κB, and MAPK pathways [36,37]. Abnormal activation of these

signaling pathways is often closely linked to the pathogenesis of IBD. IFX therapy may inhibit the activity of these signaling pathways by neutralizing TNF-α, thereby reducing IL-6 and IL-8 expression and promoting the regression of intestinal inflammation [38, 39].

Construction and verification of the nomogram model

Using logistic regression results, this study developed a predictive model to forecast IBD patients' responses to IFX treatment. The model contains the key influencing factors such as calprotectin level, ATI level, IL-6 level, and IL-8 level, and can accurately predict the response of IBD patients to IFX treatment.

To evaluate the model's predictive performance, we use ROC and calibration curves. The ROC curve analysis results show that the AUC values for calprotectin, ATI, IL-6, and IL-8 levels in this model for predicting the response of IBD patients after treatment are 0.809, 0.762, 0.850, and 0.775, respectively, indicating high predictive accuracy. The results of calibration curve analysis also indicate that the nomogram model has a good fit and can accurately predict the response of IBD patients to IFX treatment.

Discussion on the mechanism of response and loss of response: signal pathway and molecular network

Neutralization of TNF-α Signal Pathway and IFX

As an important inflammatory factor, TNF-α plays a key role in the pathogenesis of IBD. TNF-α activates downstream signaling pathways, such as the NF-κB and MAPK pathways, by binding to its cell-surface receptor, thereby inducing a series of inflammatory responses [40]. As an anti-TNF-α monoclonal antibody, IFX can specifically neutralize TNF-α, thereby blocking activation of its downstream signaling pathways. In patients receiving effective IFX treatment, inhibition of the TNF-α signaling pathway may alleviate intestinal inflammation and promote mucosal healing [41].

Interaction between calprotectin and the NF-κB signaling pathway

As mentioned above, calprotectin may be involved in the regulation of the NF-κB signaling pathway. In patients with IBD, calprotectin release may modulate NF-κB activity via unknown mechanisms, thereby indirectly influencing the expression levels of inflammatory factors. In patients with effective IFX treatment, the decrease of calprotectin level may mean the inhibition of NF-κB signaling pathway, thus reducing the production of inflammatory factors [42, 43]. This interaction may constitute an important molecular mechanism of IFX therapeutic response.

Interaction between ATI and IFX pharmacokinetics

The production of ATI can affect the pharmacokinetics of IFX in vivo. On one side, combining ATI with IFX might speed up the clearance of IFX, lowering its concentration and half-life in the body. On the other side, ATI production can also impair IFX's ability to bind to TNF-α, thereby reducing its capacity to neutralize TNF-α [44, 45]. Therefore, in patients effectively treated with IFX, decreasing ATI levels could allow IFX to sustain high biological activity and concentration in vivo, resulting in more effective neutralization of TNF-α and relief from intestinal inflammation.

Limitations and future prospects of research

Despite certain advancements, the study harbors limitations. Notably, being retrospective, it may be subject to issues such as selection and information biases. Compared with prospective cohort studies, this study is retrospective and inherently has a higher risk of selection bias and information bias. The reliance on 100 patients from a single center (Shulan Hospital) severely limited the universality of the nomogram. To overcome these limitations, we need to further increase the sample size and conduct multicenter prospective research to validate

the study's conclusions. Furthermore, the model relies solely on internal validation (Bootstrap). A robust predictive model must be validated using an independent cohort of patients (external validation) to confirm its clinical utility in different settings.

Secondly, the study examined only the effects of cytokines such as calprotectin, ATI, IL-6, and IL-8 on IFX outcomes in IBD patients, without considering other potential biomarkers or genetic factors. To fully understand the pathogenesis of IBD and the therapeutic mechanism of IFX, we need to conduct further exploration. For example, we can use gene chips, protein genomics, and other technologies to screen for additional biomarkers and apply machine learning algorithms to build multivariate predictive models [46, 47]. The application of these new technologies and methods will help us understand the pathogenesis of IBD and the therapeutic mechanism of IFX, and provide stronger support for individualized treatment.

In addition, we need to consider the long-term effects and safety of IFX in the treatment of IBD. Although IFX can significantly improve the clinical symptoms of patients in the short term, long-term use may increase the risk of infection and malignant tumors [48]. Therefore, we need to conduct long-term follow-up of patients to identify and address potential adverse reactions in a timely manner. At the same time, we need to explore additional effective treatment modalities and strategies to further improve treatment outcomes and quality of life in patients with IBD.

In sum, this study developed a predictive tool for IBD patients' IFX outcomes based on a retrospective analysis and validated its predictive performance. The results indicated that calprotectin, ATI, IL-6, and IL-8 concentrations were pivotal in determining the IFX treatment response in IBD patients. These cytokines play important roles in the pathogenesis of IBD and in the therapeutic mechanism of IFX. In the future, we need to further expand the sample size, more deeply explore the pathogenesis of IBD and the treatment mechanism of IFX, and leverage new technologies and methods to develop a more precise and stable predictive model, thereby providing a more comprehensive foundation for personalized treatment. Meanwhile, attention should be given to the long-term efficacy and safety of IFX in IBD treatment to ensure optimal patient outcomes.

Through this study, we not only identified the key determinants of IBD patients' responses to IFX treatment but also developed a predictive model with clinical applicability. This achievement provides strong support for individualized treatment of IBD and also provides an important reference for follow-up research. We believe that in the near future, as our comprehension of IBD's disease processes and IFX's therapeutic mechanisms deepens, as well as the continuous emergence of new technologies and methods, we can provide more accurate and effective treatment strategies for patients with IBD and help them get rid of the disease and regain their health and happiness.

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Consent to publish

The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

Consent to participate

We secured a signed informed consent form from every participant.

Ethic approval

This study was approved by the Ethics Committee of the Shulan (Hangzhou) Hospital, Shulan International Medical College, Zhejiang Shuren University (KY2025018)

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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RD: Edited and refined the manuscript with a focus on critical intellectual contributions. MF, JG: Participated in collecting, assessing, and interpreting the data. Made significant contributions to date interpretation and manuscript preparation. ZZ: Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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