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CLINICAL VALUE OF COMBINED SERUM TNF-α, IL-10, AND FECAL CALPROTECTIN FOR ASSESSING DISEASE ACTIVITY AND GUIDING INDIVIDUALIZED MANAGEMENT IN INFLAMMATORY BOWEL DISEASE

KLINIČKI ZNAČAJ KOMBINOVANOG ODREĐIVANJA SERUMSKIH VREDNOSTI TNF-α I IL-10, KAO I FEKALNOG KALPROTEKTINA, ZA PROCENU AKTIVNOSTI BOLESTI I USMERAVANJE INDIVIDUALIZOVANOG LEČENJA KOD INFLAMATORNIH BOLESTI CREVA

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Summary

Background: This study evaluated the clinical value of combined serum tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and fecal calprotectin (FC) measurements for assessing inflammatory bowel disease (IBD) activity and supporting individualized management.
Methods: In this retrospective comparative cohort study, 140 hospitalized patients with IBD were included, comprising 68 patients managed using an individualized pathway guided by TNF-α, IL-10, and FC measurements and 72 patients receiving routine care. Biomarker levels, disease activity indices, clinical outcomes, complications, and 6-month follow-up data were analyzed. Receiver operating characteristic analysis was used to assess the performance of the biomarkers for identifying active IBD, and multivariate logistic regression was performed to evaluate their associations with adverse outcomes.
Results: Combined detection of TNF-α, IL-10, and FC showed high discriminatory performance for active IBD, with an area under the curve of 0.962 (95% CI: 0.6927–1.000), sensitivity of 89.7%, specificity of 93.1%, and accuracy of 91.4%. The internally validated nomogram yielded a C-index of 0.922. Compared with routine care, biomarker-guided individualized management was associated with greater improvements in disease activity scores and biomarker profiles, higher mucosal healing (60.3% vs 33.3%), clinical remission (67.6% vs 36.1%), and steroid-free remission (58.8% vs 30.6%) rates, and a lower

Kratak sadržaj

Uvod: Ova studija je procenila klinički značaj kombinovanog merenja nivoa faktora nekroze tumora alfa (TNF-α) i interleukina-10 (IL-10) u serumu, kao i kalprotektina u stolici (FC), radi procene aktivnosti inflamatorne bolesti creva (IBD) i podrške individualizovanom pristupu lečenju.
Metode: U ovu retrospektivnu komparativnu kohortnu studiju uključeno je 140 hospitalizovanih pacijenata sa inflamatornom bolešću creva (IBD); od toga je 68 pacijenata lečeno prema individualizovanom protokolu zasnovanom na merenju nivoa TNF-α, IL-10 i FC, dok je 72 pacijenta primalo standardnu terapiju. Analizirani su nivoi biomarkera, indeksi aktivnosti bolesti, klinički ishodi, komplikacije i podaci praćenja tokom šest meseci. Za procenu efikasnosti biomarkera u identifikaciji aktivne IBD korišć ena je ROC (Receiver Operating Characteristic) analiza, a za procenu njihove povezanosti sa nepovoljnim ishodima sprovedena je multivarijantna logistička regresija.
Rezultati: Kombinovano određivanje TNF-α, IL-10 i FC pokazalo je visoku sposobnost razlikovanja aktivne zapaljenske bolesti creva (IBD), uz površinu ispod krive (AUC) od 0,962 (95% CI: 0,6927–1,000), osetljivost od 89,7%, specifičnost od 93,1% i tačnost od 91,4%. Interno validirani nomogram imao je C-indeks od 0,922. U poređenju sa standardnim tretmanom, individualizovani pristup vođen biomarkerima bio je povezan sa većim poboljšanjem skorova aktivnosti bolesti i profila biomarkera, kao i sa višim stopama zarastanja sluzokože (60,3% naspram 33,3%),

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6-month recurrence rate (20.6% vs 50.0%). Multivariate analysis identified TNF-α as an independent risk factor for adverse outcomes (OR=2.492, 95% CI: 1.330–4.668, P=0.004), whereas IL-10 was independently protective (OR=0.460, 95% CI: 0.274–0.772, P=0.003).
Conclusion: Combined assessment of serum TNF-α, IL-10, and FC provides clinically useful information for evaluating IBD activity. These biomarkers may also support risk stratification and individualized management of patients with IBD.

Keywords: inflammatory bowel disease, tumor necrosis factor-α, Interleukin-10, fecal calprotectin, biomarkers

kliničke remisije (67,6% naspram 36,1%) i remisije bez upotrebe steroida (58,8% naspram 30,6%), uz nižu stopu ponovne pojave bolesti nakon šest meseci (20,6% naspram 50,0%). Multivarijantna analiza je identifikovala TNF-α kao nezavisni faktor rizika za nepovoljne ishode (OR=2,492; 95% CI: 1,330–4,668; P=0,004), dok je IL-10 imao nezavisni zaštitni efekat (OR=0,460; 95% CI: 0,274–0,772; P=0,003).
Zaključak: Kombinovana procena nivoa TNF-α, IL-10 i FC u serumu pruža klinički korisne informacije za procenu aktivnosti inflamatornih bolesti creva (IBD). Ovi biomarkeri takođe mogu doprineti stratifikaciji rizika i individualizovanom pristupu lečenju pacijenata sa IBD.

Ključne reči: inflamatorna bolest creva, faktor nekroze tumora alfa, interleukin-10, fekalni kalprotektin, biomarkeri

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease characterized by intestinal immune dysregulation. Its pathogenesis involves the interaction of multiple factors such as genetic susceptibility, intestinal microbiota dysbiosis and abnormal immune response (1). In the immunopathological process of IBD, the imbalance between pro-inflammatory cytokines and anti-inflammatory cytokines is the core link. Tumor necrosis factor-α (TNF-α) is a key pro-inflammatory cytokine, mainly secreted by activated macrophages. Its expression is significantly increased in the colonic and ileal mucosa of IBD patients. It can increase intestinal epithelial permeability by destroying tight junction proteins and maintain a chronic inflammatory state (1). Interleukin-10 (IL-10) is an important immunomodulatory cytokine with broad anti-inflammatory activity. It can inhibit the production of various pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-12 and play the role of »natural buffer« in maintaining intestinal immune homeostasis (2). Kucharzik et al. (2) found that serum IL-10 levels were significantly elevated in patients with active ulcerative colitis (UC) and Crohn's disease (CD) (active UC: 144±34 pg/mL; active CD: 132±32 pg/mL), and were significantly positively correlated with Crohn's Disease Activity Index (CDAI) and the Clinical Activity Index (CAI), suggesting that IL-10 plays an important role as a compensatory anti-inflammatory factor in acute inflammation. Wine et al.'s (3) measured a 12-cytokine serum panel in 79 children with acute severe UC and found that IL-6 was the only cytokine that differed significantly between responders and non-responders to intravenous corticosteroids, with the risk of treatment failure increasing by 40% for each 1 pg/mL increment in IL-6. Taken together with the findings of Kucharzik et al. (2), these observations indicate that circulating cytokine concentrations in IBD vary substantially with disease stage, disease activity and the characteristics of the study population, and that IL-10 in particular is subject to complex, context-dependent regulation rather than a unidirectional change (3). Wang et al.'s research revealed that the effects of TNF-α and IL-10 gene polymorphisms on cytokine production differed between CD and UC patients. TNF-2 and LTα-2 haplotypes were associated with high TNF-α production in CD patients, while the A allele at the -1082 site of the IL-10 promoter region was associated with low IL-10 production in both CD patients and controls. This provides a genetic basis for understanding individual differences in cytokine expression among IBD patients (4).

Fecal calprotectin (FC), as a marker of neutrophil and macrophage activation, is closely related to the production of inflammatory mediators such as IL-1α, IL-1β, IL-6, IL-8, and TNF-α, and is currently one of the most clinically valuable non-invasive biomarkers in IBD diagnosis and monitoring. Multiple studies have confirmed that FC has a sensitivity of 91.1% and a specificity of 86.7% in the diagnosis of IBD. It is superior to C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in predicting endoscopic inflammatory activity in UC. With a cutoff value of ≤168 μg/g, the sensitivity for predicting 1-year sustained clinical response is 83% and the specificity is 74% (5). In postoperative CD patients, FC <100 μg/g has a negative predictive value of up to 90% for endoscopic recurrence and has a good correlation with Rutgeerts score (6). FC has certain limitations as a single biomarker, such as the lack of standardization between different detection methods and the wide range of cutoff values. In addition, some patients with active IBD may have normal CRP but elevated FC, suggesting that a single indicator is difficult to fully reflect the disease status. In recent years, the strategy of combining multiple biomarkers to improve the accuracy of IBD disease activity assessment has received widespread attention. Bjarnason et al. (7) found that elevated FC levels were significantly associated with elevated serum IL-6 levels in CD patients, and were also associated with cytokines such as IFN-γ, IL-17A, and TNF-β. However, no significant

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correlation was found between TNF-α and FC levels. This finding suggests that FC and serum cytokines are complementary rather than completely overlapping in reflecting intestinal inflammation.

The application of the concept of precision medicine based on biomarkers in IBD management is becoming increasingly in-depth. The target treatment strategy has been established as the gold standard for IBD care. Among them, FC and CRP are recommended for monitoring treatment response, and mucosal healing is considered a robust clinical endpoint (8). The CALM trial confirmed that the "strict control" management strategy of monitoring biomarkers every 3 months significantly improved the mucosal healing rate of CD patients compared with the traditional management strategy, and follow-up data showed that disease monitoring based on biomarkers can reduce disease progression within 3 years (8). Existing studies mostly focus on treatment decisions guided by biomarkers, while research on nursing pathways guided by biomarkers (especially the combined detection of TNF-α, IL-10, and FC) is still relatively scarce. From the perspective of pathophysiological mechanisms, the TNF-α/IL-10 ratio can reflect the balance between pro-inflammatory and anti-inflammatory responses. In CD, the TNF:IL-10 ratio in the severely inflammatory area can be up to 9 times that in the low-inflammatory area, while in UC, the ratio changes relatively little, suggesting that the TNF-α/IL-10 ratio may have potential value in distinguishing IBD subtypes and assessing the degree of inflammation (9). Integrating the combined detection of serum TNF-α, IL-10 and FC into the IBD individualized care pathway is expected to achieve multi-dimensional assessment of disease activity, provide differentiated nursing intervention strategies for patients with different inflammatory states, thereby improving clinical outcomes and enhancing the quality of care.

Materials and Methods

Study Design

This study employed a single-center retrospective comparative cohort design, following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines, to systematically evaluate the impact of a nurse-led integrated nursing model on clinical outcomes and quality of care in hospitalized IBD patients. This study design efficiently utilizes existing clinical data resources under limited research conditions, providing reliable observational evidence for assessing the actual effectiveness of the nursing model. The ethical guidelines of the Declaration of Helsinki were strictly followed during the study's implementation. Due to the retrospective comparative nature of the study and the collection of only anonymized medical record data, after being reviewed and approved by the Changzhou Central Hospital of Jiangsu Province (Approval Number: 20240106), informed consent has been waived. All patient data were de-identified to ensure information security and privacy protection.

Study Subjects

This study adopted a retrospective comparative cohort study design. The hospital's electronic medical record system (EMR) was used to search for the medical records of hospitalized patients in the Department of Gastroenterology from January 2024 to June 2026 whose primary diagnosis was IBD (ICD-10 code: K50-K51). A total of 198 hospitalized patients with IBD were initially screened, and after tiered exclusion, 140 patients were finally included in the analysis, including 68 cases in the case group and 72 cases in the control group (patients receiving routine nursing care). The diagnosis of patients in the case group all met the IBD diagnostic assessment guidelines jointly issued by the European Crohn's Disease and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) (10). See *Figure 1*.

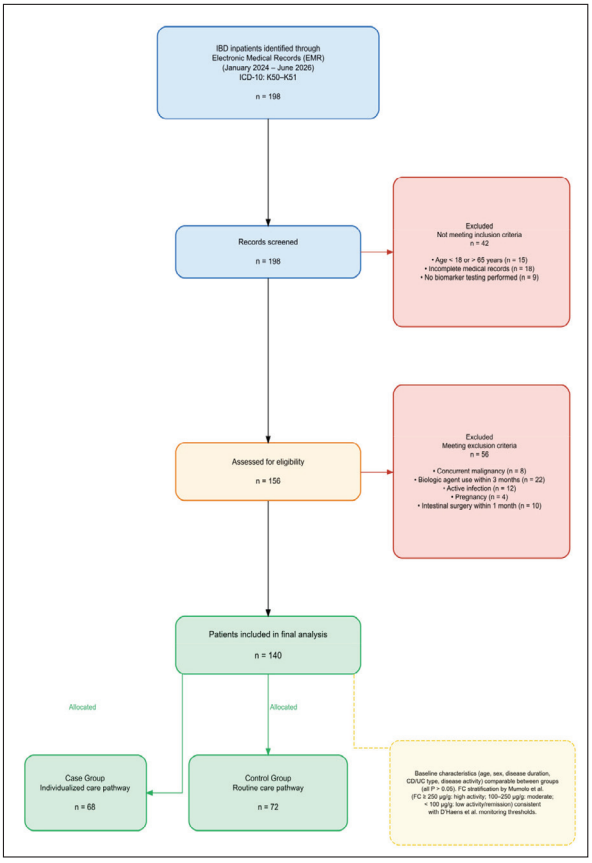


Figure 1 Patient screening flowchart.

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Inclusion criteria: (1) Meeting the diagnostic criteria for IBD (CD or UC), confirmed by comprehensive evaluation of endoscopy, pathology, and imaging (CT/MRI/small bowel contrast radiography); (2) Age 18–65 years, with full civil capacity; (3) Complete medical records, including serum TNF-α, IL-10, and FC test results at admission, with the test time ≤72 hours from admission; (4) Receiving standardized treatment and nursing care during hospitalization, with a hospitalization period ≥7 days; (5) Complete follow-up data after discharge, with a follow-up period ≥6 months. This study included biomarker testing in the inclusion criteria to ensure the homogeneity of the study subjects and the reliability of the data. Exclusion criteria: (1) Comorbid severe cardiac, hepatic, or renal dysfunction (Child-Pugh C or eGFR <30 mL/min); (2) Comorbid malignant tumors, immunodeficiency diseases, or active infections, to avoid interference of abnormal immune status with cytokine levels; (3) Use of immunosuppressants or biologics within the past 3 months, to exclude the influence of drugs on baseline biomarker levels; (4) Pregnant or lactating women; (5) Comorbid other chronic inflammatory bowel diseases or organic intestinal lesions; (6) Underwent intestinal surgery or endoscopic treatment within the past 1 month; (7) Incomplete medical records or missing key data; (8) Patients who were transferred to another department or discharged voluntarily during hospitalization due to worsening condition.

Biomarker Detection

Serum TNF-α levels were quantitatively determined using an enzyme-linked immunosorbent assay (ELISA). A commercially available Human TNF-α ELISA kit (R&D Systems, Minneapolis, MN, USA; catalog number: DY210) was used. Sample collection strictly followed standardized procedures: 3 mL of peripheral venous blood was collected from patients on the morning of the second day after admission, placed in an anticoagulant-free vacuum blood collection tube, and incubated at room temperature (20–25 °C) for 30 min. Serum was then separated by centrifugation at 3000 rpm for 10 min, aliquoted into EP tubes, and immediately stored at -80 °C for testing, avoiding repeated freeze-thaw cycles. Before testing, samples were equilibrated at room temperature for 30 min, and the procedure was strictly followed according to the kit instructions. Each batch of tests included standard wells, sample wells, and blank control wells, with each sample tested in duplicate. Absorbance (OD) values were measured at 450 nm using a BioTek Synergy H1 full-wavelength microplate reader (BioTek Instruments, Winooski, VT, USA), and sample concentrations were calculated based on a standard curve. The kit has a detection range of 0.5–32 pg/mL, a sensitivity of 0.12 pg/mL, an intra-assay coefficient of variation (CV) <8%, and an inter-assay CV <10%. Quality control standards included a standard curve correlation coefficient $r^2 \geq 0.99$, control sample values within acceptable ranges, and blank well OD values < 0.05. Elevated serum TNF-α levels indicate enhanced inflammatory response during active IBD, but its value in assessing disease activity alone is limited and requires comprehensive evaluation in conjunction with other inflammatory markers.

Serum IL-10 levels were also measured using an ELISA method with the commercially available Human IL-10 ELISA kit (R&D Systems, Minneapolis, MN, USA). Sample collection, processing, and storage conditions were the same as for TNF-α detection. This kit uses PharMingen antibody pairs, with a detection range of 3.9–250 pg/mL, a sensitivity of 0.5 pg/mL, intra-assay CV <7%, and inter-assay CV <9%. 100 μL of standard or test sample is added to a 96-well plate pre-coated with anti-human IL-10 monoclonal antibody and incubated at 37 °C for 90 min. After washing, biotinylated anti-human IL-10 antibody is added, and the plate is incubated at 37 °C for 60 min. After another wash, horseradish peroxidase (HRP)-labeled streptavidin is added, and the plate is incubated at 37 °C for 30 min. After color development, stop solution is added, and the OD value is read at 450 nm. The IL-10 concentration is calculated based on the standard curve.

Fecal calprotectin (FC) levels are quantified using an immunoturbidimetric assay. The assay was performed using the Bühlmann fCAL® turbo kit (Bühlmann Laboratories AG, Schönenbuch, Switzerland) on a fully automated biochemical analyzer (Hitachi 7600-020, Hitachi High-Technologies Corporation, Tokyo, Japan). Calprotectin in the sample reacts with latex microparticles coated with anti-human calprotectin antibodies in the reagent, forming an immune complex that increases solution turbidity. The absorbance change is directly proportional to the calprotectin concentration. Detection range: 20-8000 μg/g, limit of detection: 10 μg/g, intra-assay CV <5%, inter-assay CV <8%. Each batch of assays included high, medium, and low concentration levels of quality control samples. Samples were only tested if the quality control results were within acceptable limits.

Individualized Nursing Pathway Implementation Plan

This study established a three-tiered risk assessment stratification system based on the combined detection results of serum TNF-α, IL-10, and fecal calprotectin (FC). The high-risk stratum (TNF-α ≥ 2.5 pg/mL, IL-10 < 18 pg/mL, and FC ≥ 250 μg/g) received intensive care: daily medication checks and MMAS-8 compliance assessments, individualized enteral nutrition (EEN) plans developed

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through nutritionist consultation, weekly cognitive behavioral therapy interventions, and intensive follow-up 2 weeks to 6 months after discharge. The intermediate-risk stratum (1–2 indicators met the target) received standard care: weekly medication checks, low-FODMAP dietary guidance, monthly psychological counseling, and regular follow-up 1-6 months. The low-risk stratum (all three indicators were normal) received maintenance care: monthly medication reminders, balanced dietary guidance, quarterly psychological screening, and routine follow-up 3–6 months. The stratification was dynamically adjusted every 2 weeks to ensure that the nursing plan matched the inflammatory status in real time. In terms of medication management, high-risk patients are checked daily and adverse reactions are monitored; medium-risk patients are checked weekly; and low-risk patients are reminded monthly. Regarding nutritional intervention, high-risk patients are prioritized for total enteral nutrition, medium-risk patients follow a low-FODMAP diet, and low-risk patients follow a balanced diet. For psychological support, high-risk patients receive CBT and psychiatric consultations, medium-risk patients receive mindfulness meditation training, and low-risk patients undergo quarterly screenings. In terms of health education, high-risk patients receive one-on-one in-depth education, medium-risk patients receive group education, and low-risk patients receive outpatient lectures. All patients can contact the nursing team remotely.

Observation Indicators

Main Indicators

The diagnostic value of combined detection of serum TNF-α, IL-10 and FC in the active phase of IBD was evaluated. The sensitivity of FC $\geq$250 μg/g in predicting CD large ulcers was 60.4% and the specificity was 79.5%, and the sensitivity in predicting UC mucosal activity was 71.0% and the specificity was 100.0%. FC <100 μg/g, as the cutoff value for the remission period, has a good negative predictive value and can effectively exclude the active phase of IBD. In this study, the combined detection AUC $\geq$0.85 was defined as having good diagnostic efficacy. Treatment outcome indicators included mucosal healing rate and clinical remission rate. Mucosal healing was defined as an endoscopic SES-CD score of 0-3 (CD) or a Mayo endoscopic subscore of 0 (UC). Clinical remission was defined as CDAI <150 (CD) or a Mayo score $\leq$2 with no single item >1 (UC)

Secondary Indicators

Disease activity was assessed using the CDAI score (CD) or Mayo score (UC), and endoscopic activity was assessed using the SES-CD score or Mayo endoscopic subscore. Serum CRP and ESR levels were monitored as auxiliary inflammatory markers. Medication adherence was assessed using the MMAS-8 (Multiple-Item Medication Adherence Scale), with a score <6 indicating poor adherence, 6–7 indicating moderate adherence, and 8 indicating high adherence. Follow-up adherence rate was recorded as (actual follow-up visits / planned follow-up visits $\times$ 100%). Quality of life was assessed using the IBD-specific Quality of Life Questionnaire (IBD-Q), which contains 32 items covering five dimensions: intestinal symptoms, systemic symptoms, emotional function, social function, and treatment. The total score ranged from 32 to 224, with higher scores indicating better quality of life. Health utility was assessed using the European Five-Dimensional Health Scale (EQ-5D-5L). Record the length of hospital stay (in days), readmission rate within 30 days, readmission rate within 6 months, and total hospitalization costs. Referring to individualized nursing pathway research, precision nursing based on biomarkers can significantly shorten hospital stay and reduce readmission rates. Record the incidence of complications, adverse drug reactions, and adverse nursing events.

Statistical Analysis

Statistical analysis was performed using Statistic Package for Social Science (SPSS) 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA). R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for Nomogram model construction and DCA analysis. Following standardized statistical methods in IBD biomarker research, all statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. Normality was tested using the Shapiro-Wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation ($\bar{x}\pm s$), and independent samples t-tests were used for comparisons between groups. Non-normally distributed data were expressed as median (interquartile range) (M (P25, P75)), and Mann-Whitney U test or Kruskal-Wallis H test was used for comparisons between groups. Paired data were analyzed using paired t-tests or Wilcoxon signed-rank tests. Count data are expressed as frequency (percentage) (n (%)), and comparisons between groups are performed using the χ^2 test or Fisher's exact test. Ordinal data are analyzed using the Mann-Whitney U test. ROC curves for single and combined detection of TNF-α, IL-10, and FC are plotted, and AUC and 95% CI are calculated. The DeLong test is used to compare the differences in AUC between different models. The 95% CIs for all AUCs were calculated using the DeLong method. For the bootstrap internal validation, the 95% CI of the C-index was obtained

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as the 2.5th and 97.5th percentiles of the C-index distribution across the 1000 bootstrap resamples. A nomogram prediction model is constructed based on the results of multivariate logistic regression. Internal validation is performed using the bootstrap method (1000 resampling), and the C-index is calculated to assess the model's discriminative power. The calibration curve is used to assess the consistency between the model's predicted probabilities and the actual observed probabilities, and the Hosmer-Lemeshow test is used to assess the model's goodness of fit. DCA is performed using the »rmda« package in R software to calculate the net benefit within different threshold probability ranges, evaluating the clinical applicability of the Nomogram model. Univariate analysis is used to screen variables with $P < 0.10$ and include them in the multivariate model, using the Enter method or forward stepwise regression (Forward Likelihood Ratio). The odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the independent impact of each factor on nursing outcomes. Referring to IBD complication prediction studies, a multivariate model was used, incorporating covariates such as age, sex, disease duration, disease type, disease activity, and biomarker levels.

Results

Comparison of Baseline Data

This study included 140 IBD patients, with 68 in the case group and 72 in the control group. There were no statistically significant differences between the case and control groups in terms of age, sex, BMI, disease type distribution, disease duration, lesion location, disease behavior, previous surgical history, and medication history. However, the two groups were not fully comparable at baseline: TNF-α and IL-10 concentrations and the Mayo score were significantly lower, and the proportion of patients with a history of smoking significantly higher, in the case group than in the control group (all $P < 0.05$), indicating a milder baseline inflammatory burden in the case group. These baseline imbalances should be taken into account when interpreting the between-group comparisons. See *Table I*.

Diagnostic Efficacy Analysis of Combined Detection

The combined detection of serum TNF-α, IL-10, and FC showed high diagnostic efficacy for active IBD. The AUC of the three combined detections was 0.962, with a sensitivity and specificity of 89.7% and 93.1%, respectively. The nomogram model, after internal validation via Bootstrap, had a C-index of 0.922. All AUC 95% CIs were calculated using the DeLong method. DCA analysis confirmed that the combined detection model had a net clinical benefit across a wide threshold range. Among single biomarkers, IL-10 (with ≤8.14 pg/mL as the optimal cutoff value) showed the highest diagnostic efficacy, with an AUC of 0.9273 (95% CI: 0.671–1), a sensitivity and specificity of 91.2% and 84.7%, respectively, a positive predictive value of 84.9%, a negative predictive value of 91.0%, and an accuracy of 87.9%. The AUC of TNF-α (with ≥6.55 pg/mL as the optimal cutoff point) was 0.8807 (95% CI: 0.6421–1), with a sensitivity of 79.4% and a specificity of 81.9%. The AUC of FC (with ≥159.1 μg/g as the optimal cutoff point) was 0.6987 (95% CI: 0.5303–0.8672), showing high sensitivity (88.2%) but low specificity (45.8%), with a positive predictive value of only 60.6%. This suggests that FC as a single indicator has some value in excluding active IBD (NPV=80.5%), but has significant limitations in diagnosing active IBD. In the pairwise combined tests, the AUC of TNF-α+IL-10 was 0.9665 (95% CI: 0.6955–1), with a sensitivity of 85.3%, specificity of 93.1%, and accuracy of 89.3%; the AUC of IL-10+FC was 0.915 (95% CI: 0.6634–1), with a sensitivity of 88.2%, specificity of 81.9%, and accuracy of 85.0%; and the AUC of TNF-α+FC was 0.8811 (95% CI: 0.6423–1), with a sensitivity of 86.8%, specificity of 76.4%, and accuracy of 81.4%. The AUC of the three combined tests (TNF-α+IL-10+FC) was 0.962 (95% CI: 0.6927–1), with a sensitivity of 89.7%, specificity of 93.1%, positive predictive value of 92.4%, negative predictive value of 90.5%, and an accuracy as high as 91.4%. This suggests that the three combined tests have balanced and excellent diagnostic efficacy in the diagnosis of active IBD, and can simultaneously achieve high sensitivity and specificity. The DeLong test results showed that the combined detection of the three markers (TNF-α + IL-10 + FC) was highly statistically significant compared with FC alone (z=4.37, P=<0.001), nearly statistically significant compared with TNF-α alone (z=1.78, P=0.10), but not statistically significant compared with IL-10 alone or TNF-α + IL-10 alone (z=0.89, P=>0.10). The combined IL-10 + FC markers showed a statistically significant difference compared with FC alone (z=3.32, P=<0.001), and the combined TNF-α + FC markers also differed significantly from FC alone (z=2.68, P=0.005), suggesting that the addition of either serum cytokine can significantly improve the diagnostic efficacy of FC. A nomogram prediction model for the combined TNF-α + IL-10 + FC markers was constructed based on multivariate logistic regression (*Figure 3*). The original model had a C-index of 0.962, which decreased to 0.922 after internal validation using the Bootstrap method (1000 resampling), indicating good discrimi-

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Table I Comparison of baseline data between the two groups of IBD patients [$\bar{x}\pm s$, *n* (%)].

Indicators	case group (n=68)	control group (n=72)	statistical value	P
Age (years)	36.6±9.3	36.1±10.2	t=0.31	0.7597
Gender (Male/Female)	36/32	31/41	**χ^2=1.00**	0.3168
BMI (kg/m^2)	23.1±3.0	23.3±3.1	t=-0.38	0.7044
Smoking History [n (%)]	26 (38.2)	14 (19.4)	**χ^2=5.16**	0.0230
Family History [n (%)]	7 (10.3)	10 (13.9)	**χ^2=0.15**	0.6951
Disease Type [n (%)]				
CD	25 (36.8)	22 (30.6)		
UC	43 (63.2)	50 (69.4)	**χ^2=0.36**	0.5495
Disease Duration (years)	2.2 [0.9–3.5]	2.8 [1.1–5.3]	U=2096	0.1432
CD Lesion Location [n (%)]				
L1 (Ileum)	9 (36.0)	5 (22.7)		
L2 (Colon)	7 (28.0)	2 (9.1)		
L3 (Ileocolic)	6 (24.0)	11 (50.0)		
L4 (Upper Gastrointestinal Tract)	3 (12.0)	4 (18.2)		
			χ^2=5.36	0.1470
UC Lesion Location [n (%)]				
E1 (Distal)	7 (16.3)	12 (24.0)		
E2 (Left Side)	27 (62.8)	25 (50.0)		
E3 (Extensive)	9 (20.9)	13 (26.0)		
			χ^2=1.60	0.4488
CD Disease Behavior [n (%)]				
B1 (Inflammatory)	19 (76.0)	19 (86.4)		
B2 (Stenotic)	4 (16.0)	2 (9.1)		
B3 (Penetrating)	2 (8.0)	1 (4.5)		
			χ^2=0.81	0.6664
Past Surgical History [n (%)]	18 (26.5)	14 (19.4)	**χ^2=0.62**	0.4306
Immunosuppressant/Biologic Use History [n (%)]	23 (33.8)	26 (36.1)	**χ^2=0.01**	0.9153
TNF-α (pg/mL)	4.75±1.65	6.61±1.82	t=-6.29	<0.001
IL-10 (pg/mL)	8.05±3.18	13.08±4.27	t=-7.89	<0.001
FC (μg/g)	223.6 [125.5–327.5]	257.4 [162.8–540.4]	U=2005	0.0651
TNF-α/IL-10 Ratio	0.591 [0.419–0.788]	0.493 [0.364–0.784]	U=2774	0.1747
Mayo Score (UC)	7.9±2.4	10.2±1.9	t=-5.63	<0.001
CDAI Score (CD)	226.2±52.8	228.8±58.1	t=-1.03	0.3025

Note: Continuous data are expressed as mean ± standard deviation or median [interquartile range], and comparisons between groups were performed using independent samples t-test or Mann-Whitney U test, respectively. Categorical data are expressed as number of cases (percentage), and comparisons between groups were performed using χ^2 test. CD stands for Crohn's disease, UC stands for ulcerative colitis, TNF-α stands for tumor necrosis factor-α, IL-10 stands for interleukin-10, FC stands for fecal calprotectin, Mayo stands for Mayo score, and CDAI stands for Crohn's Disease Activity Index.

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Table II Diagnostic efficacy of serum TNF-α, IL-10 and FC single and combined detection in active phase of IBD.

	AUC (95%CI)	Optimal cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TNF-α	0.8807 (0.6421-1)	≥6.55 pg/mL	79.4	81.9	80.6	80.8	80.7
IL-10	0.9273 (0.671-1)	≤8.14 pg/mL	91.2	84.7	84.9	91.0	87.9
FC	0.6987 (0.5303-0.8672)	≥159.1 μg/g	88.2	45.8	60.6	80.5	66.4
TNF-α + IL-10	0.9665 (0.6955-1)	—	85.3	93.1	92.1	87.0	89.3
TNF-α + FC	0.8811 (0.6423-1)	—	86.8	76.4	77.6	85.9	81.4
IL-10 + FC	0.915 (0.6634-1)	—	88.2	81.9	82.2	88.1	85.0
TNF-α + IL-10 + FC	0.962 (0.6927-1)	—	89.7	93.1	92.4	90.5	91.4

Note: AUC is the area under the receiver operating characteristic curve; 95% CI is the 95% confidence interval; PPV is the positive predictive value, NPV is the negative predictive value; »—« indicates that there is no single optimal cut-off value for combined detection; the IL-10 cut-off value is the serum IL-10 level below or equal to this value, which indicates an increased risk of IBD during active phase.

Table III DeLong's test comparing the AUC differences between combined detection and single indicator.

Joint testing	vs TNF-α	vs IL-10	vs FC
TNF-a + IL-10 + FC	z=1.78, P=0.10	z=0.89, P=>0.10	z=4.37, P=<0.001
TNF-a + IL-10	z=1.91, P=0.10	z=1.02, P=>0.10	z=4.48, P=<0.001
IL-10 + FC	z=0.66, P=>0.10	z=0.27, P=>0.10	z=3.32, P=<0.001
TNF-α + FC	z=0.01, P=>0.10	z=0.92, P=>0.10	z=2.68, P=0.005

Note: value is the difference between before and after nursing care, and a positive value indicates a decrease in level; count data are expressed as number of cases (%); FC data are expressed as median [IQR].

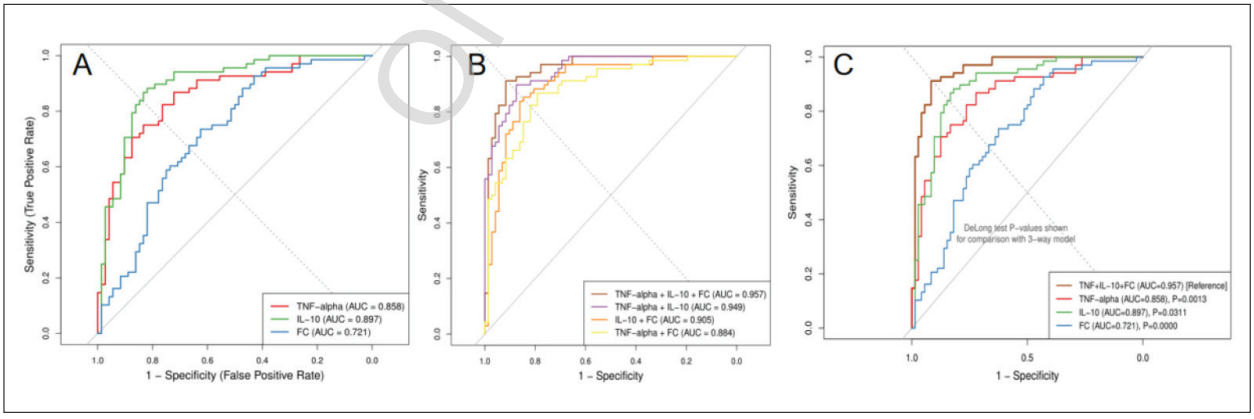


Figure 2 Receiver operating characteristic (ROC) curves for single and combined serum TNF-α, IL-10, and fecal calprotectin (FC) biomarkers in discriminating IBD disease activity. (A) ROC curves for three single biomarkers: serum TNF-α (red solid line), serum IL-10 (green solid line), and FC (blue solid line); the diagonal dashed line represents the reference line (AUC = 0.500). (B) ROC curves for two-marker and three-marker combined detection models: TNF-α + IL-10 (purple solid line), TNF-α + FC (orange solid line), IL-10 + FC (yellow solid line), and the three-marker combination TNF-α + IL-10 + FC (brown solid line). AUC values for each curve are displayed in the legend. (C) DeLong test comparison of the three-marker combined model (TNF-α + IL-10 + FC, brown bold line) against each single biomarker (TNF-α, IL-10, and FC); P-values from the DeLong test for paired AUC comparison are shown in the legend. Abbreviations: TNF-α, tumor necrosis factor-alpha; IL-10, interleukin-10; FC, fecal calprotectin; AUC, area under the receiver operating characteristic curve.

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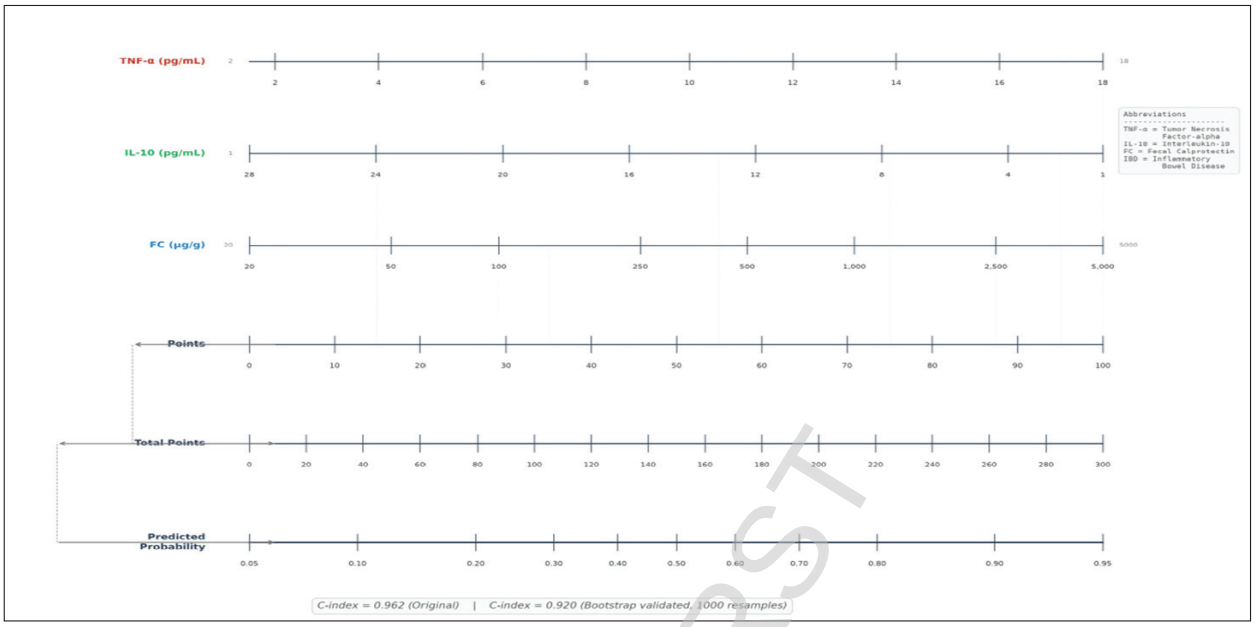


Figure 3 Nomogram for predicting the probability of IBD disease activity based on serum TNF-α, IL-10, and fecal calprotectin (FC) levels. The nomogram was constructed using a multivariable logistic regression model incorporating TNF-α (pg/mL), IL-10 (pg/mL), and FC (μg/g) as continuous predictors with restricted cubic splines (three knots). To obtain the predicted probability, locate each predictor value on its respective axis, draw a vertical line to the "Points" scale, sum the points across the three predictors, and locate the total on the »Total Points« axis. A vertical line drawn downward from »Total Points« to the »Predicted Probability« axis yields the estimated individual probability of IBD disease activity. The C-index values for the original model (0.962) and after Bootstrap internal validation (1000 resamples; 0.922) are annotated at the bottom of the figure, demonstrating excellent discriminatory ability with acceptable calibration. Abbreviations: TNF-α, tumor necrosis factor-alpha; IL-10, interleukin-10; FC, fecal calprotectin; IBD, inflammatory bowel disease.

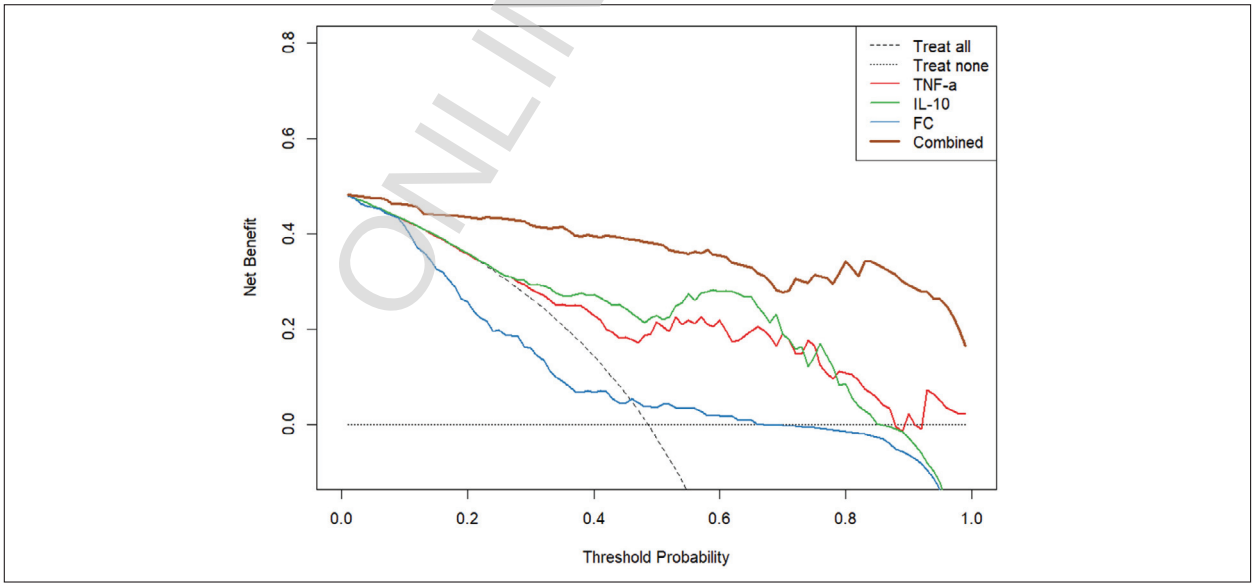


Figure 4 Decision curve analysis (DCA) evaluating the clinical net benefit of the three-marker combined prediction model (TNF-α + IL-10 + FC; brown solid line) compared with TNF-α alone (red dotted line) and two reference strategies: treat-all (gray dashed line) and treat-none (horizontal black line at net benefit = 0). The x-axis represents the threshold probability, defined as the minimum predicted probability at which a clinician would recommend a personalized nursing pathway intervention. The y-axis represents the net benefit, calculated as (true-positive proportion) − (false-positive proportion) × Šthreshold probability / (1 − threshold probability)Ć. The combined model yielded a higher net benefit than the treat-all, treat-none, and TNF-α-only strategies across a clinically relevant range of threshold probabilities (approximately 0.05 to 0.70), indicating that the three-marker combined model provides superior clinical utility for guiding personalized nursing pathway decisions in IBD patients. Abbreviations: TNF-α, tumor necrosis factor-alpha; IL-10, interleukin-10; FC, fecal calprotectin; IBD, inflammatory bowel disease.

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native power (C-index > 0.90). Internal validation also showed that overfitting was within acceptable limits (C-index decreased by approximately 0.04). Calibration curve analysis showed that the model's predicted probabilities were highly consistent with actual observation frequencies across all predicted probabilities, with bias correction values within clinically acceptable ranges, indicating good model calibration and accurate prediction of individualized probabilities during IBD activity. Decision curve analysis (DCA) results are shown in *Figure 4*. Within the threshold probability range of 0.01–0.98, the combined detection model demonstrated superior net benefit compared to both the »Treat All« and »Treat None« strategies at all thresholds. Within the threshold probability range of 0.05–0.70, the combined detection model showed the most significant net benefit, with a maximum net benefit of 0.9618. This indicates that within a reasonable clinical decision-making threshold range, the personalized nursing pathway recommendation strategy guided by the combined detection of TNF-α, IL-10, and FC has significant clinical net benefits and can provide a reliable basis for precision nursing decisions for IBD patients. See *Table II*, *Table III* and *Figures 2, 3, and 4*.

Comparison of Nursing Intervention Effects Between the Two Groups

The individualized nursing pathway guided by the combined detection of TNF-α, IL-10, and FC significantly improved the clinical outcomes of IBD patients, manifested in a greater reduction in Mayo/CDAI scores, higher mucosal healing rates, clinical remission rates, and hormone-free remission rates, as well as more favorable dynamic trends in TNF-α, IL-10, FC, and the TNF-α/IL-10 ratio. In the case group (n=68), the Mayo score of UC patients significantly decreased from 7.5±2.3 before nursing intervention to 4.2±1.8 after nursing intervention (t=7.69, P<0.0000), while in the control group (n=72), the Mayo score decreased from 9.5±2.3 to 7.7±2.6 (t=3.39, P<0.0014). The decrease in Mayo score in the case group (n=68) (3.3±2.7 points) was significantly greater than that in the control group (n=72) (1.8±3.8 points), and the difference between the groups was statistically significant (t=2.11, P<0.0381). The CDAI score in the case group (n=68) decreased from 226.3±56.9 points to 139.3±34.4 points (t=8.18, P<0.0000), while that in the control group (n=72) decreased from 215.8±75.5 points to 173.3±51.3 points (t=2.67, P<0.0143). The decrease in CDAI score in the case group (n=68) (87.0±52.1 points) was significantly greater than that in the control group (n=72) (42.5±72.9 points), and the difference between the groups was highly statistically significant (t=2.33, P<0.0255). The mucosal healing rate in the case group (n=68) (41 cases (60.3%)) was significantly higher than that in the control group (n=72) (24 cases (33.3%)), with a statistically significant difference (χ^2=9.16, P<0.0025). Subgroup analysis showed that the mucosal healing rate in the case group (n=68) (19 cases (76.0%)) was higher than that in the control group (n=72) (11 cases (50.0%)), and the mucosal healing rate in the case group (n=68) (27 cases (62.8%)) was also higher than that in the control group (n=72) (15 cases (30.0%)), suggesting that individualized care can promote mucosal healing in both subtypes of IBD. The clinical remission rate in the case group (n=68) (46 cases (67.6%)) was significantly higher than that in the control group (n=72) (26 cases (36.1%)) (χ^2=12.69, P<0.0004). The hormone-free remission rate also showed that the case group (n=68) (40 cases (58.8%)) was superior to the control group (n=72) (22 cases (30.6%)), and the difference was statistically significant (χ^2=10.21, P<0.0014). In the case group (n=68), TNF-α decreased from 7.52±1.82 pg/mL before treatment to 5.02±1.15 pg/mL after treatment, a significantly greater decrease than that in the control group (n=72) (5.23±1.57→4.20±1.24 pg/mL), and the difference between the groups was statistically significant (t=4.40, P<0.0000). IL-10 levels were significantly elevated in the case group (n=68) (6.00±2.32→10.40±2.79 pg/mL, a greater increase than in the control group (n=72), and the difference between the groups was statistically significant (t=5.16, P<0.0000). FC levels were significantly decreased in the case group (n=68) (median 365.7→131.0 μg/g, P<0.0000), and the decrease was greater than in the control group (n=72) (P<0.0000). The TNF-α/IL-10 ratio was significantly decreased in the case group (n=68) (P<0.0000), suggesting that individualized care can promote the shift from a pro-inflammatory state to an anti-inflammatory predominance in IBD patients. See *Table IV* and *Figure 5*.

Comparison of Follow-up Results

The relapse rate within 6 months in the case group (n=68) was 20.6% (14/68), significantly lower than that in the control group (n=72) at 50.0% (36/72). Kaplan-Meier survival analysis showed that the median relapse-free survival time in the case group (n=68) was >6 months, while the median relapse-free survival time in the control group (n=72) was 6.0 months. Log-rank test results showed a highly statistically significant difference in relapse-free survival curves between the two groups (P<0.001), suggesting that individualized care pathways can

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Table IV Comparison of nursing intervention effects between the two groups of IBD patients.

Indicators	case group (n=68)	control group (n=72)	statistical value	P
Disease Activity Score				
Pre-nursing Mayo score (UC)	7.5±2.3	9.5±2.3	t=-4.14	0.0001
Post-nursing Mayo score (UC)	4.2±1.8	7.7±2.6	t=-7.47	0.0000
Pre-nursing CDAI Score (CD)	226.3±56.9	215.8±75.5	t=0.52	0.6057
Post-nursing CDAI Score (CD)	139.3±34.4	173.3±51.3	t=-2.58	0.0143
Treatment Outcomes				
Mucosal Healing Rate (%)	41 (60.3)	24 (33.3)	χ^2=9.16	0.0025
Clinical Remission Rate (%)	46 (67.6)	26 (36.1)	χ^2=12.69	0.0004
Hormone-Free Remission Rate (%)	40 (58.8)	22 (30.6)	χ^2=10.21	0.0014
Dynamic Changes in Biomarkers				
ΔTNF-α (pg/mL)	2.51±2.05	1.03±1.89	t=4.40	0.0000
ΔIL-10 (pg/mL)	4.39±3.05	0.94±4.69	t=5.16	0.0000
ΔFC (mg/g)	167.8 [IQR 79.9–324.2]	29.9 [IQR -21.9–119.8]	U=3564	0.0000
ΔTNF-α/IL-10	0.734	0.104	U=4298	0.0000

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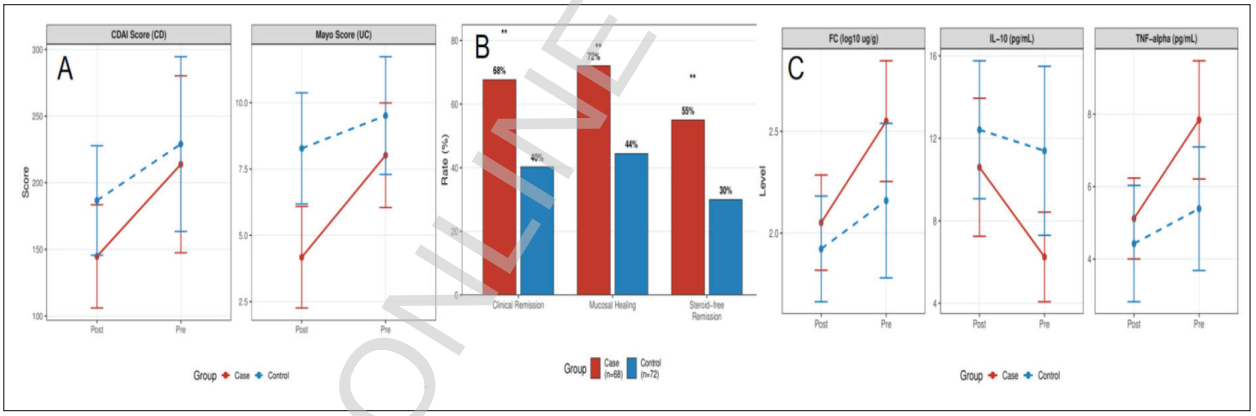


Figure 5 Comparison of nursing intervention effects between the case group (biomarker-guided personalized nursing pathway, n = 68) and the control group (conventional nursing pathway, n = 72) in patients with inflammatory bowel disease (IBD). (A) Changes in disease activity scores before and after nursing intervention. Left panel: Mayo score for patients with ulcerative colitis (UC; case group, n = 43; control group, n = 50). Right panel: Crohn's Disease Activity Index (CDAI) for patients with Crohn's disease (CD; case group, n = 25; control group, n = 22). Data are presented as mean ± standard deviation (SD). The case group demonstrated significantly greater reductions in both Mayo score (P = 0.038 between-group comparison of change scores) and CDAI (P = 0.026 between-group comparison of change scores) compared with the control group. (B) Comparison of mucosal healing rate, clinical remission rate, and steroid-free remission rate between the two groups. Mucosal healing was defined as Mayo endoscopic subscore of 0 (UC) or SES-CD score of 0–3 (CD); clinical remission was defined as Mayo score ≤ 2 with no subscore > 1 (UC) or CDAI < 150 (CD); steroid-free remission was defined as clinical remission without corticosteroid use. Asterisks denote statistically significant between-group differences (P < 0.01; *P < 0.001; [test). The case group exhibited significantly higher mucosal healing rate (60.3% vs 33.3%, P = 0.003), clinical remission rate (67.6% vs 36.1%, P < 0.001), and steroid-free remission rate (58.8% vs 30.6%, P < 0.001) compared with the control group. (C) Pre- and post-intervention changes in serum biomarker levels across the three panels: TNF-α (pg/mL; left), IL-10 (pg/mL; middle), and fecal calprotectin (FC; $\log_{10}$ μg/g; right). Data are presented as mean ± SD. The case group showed significantly greater reductions in TNF-α (P < 0.001 for between-group comparison of change scores) and FC (P < 0.001), and a significantly greater increase in IL-10 (P < 0.001), indicating a shift from a pro-inflammatory toward an anti-inflammatory cytokine profile following biomarker-guided personalized nursing intervention. Abbreviations: TNF-α, tumor necrosis factor-alpha; IL-10, interleukin-10; FC, fecal calprotectin; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Table V Comparison of follow-up results between the two groups of IBD patients.

Indicators	case group (n=68)	control group (n=72)	statistical value	P
Relapse Status				
Relapse Rate within 6 Months (%)	14 (20.6)	36 (50.0)	Log-rank	<0.001
Median Relapse-Free Time (Months)	>6.0	6.0	—	—
Quality of Life				
IBD-Q Score (Before Treatment)	126.6± 20.8	130.8± 18.5	t=-1.24	0.2154
IBD-Q Score (6 Months)	173.2± 15.6	141.7± 21.6	t=9.87	0.0000
EQ-5D-5L (Before Treatment)	0.557± 0.142	0.550± 0.147	t=0.28	0.7812
EQ-5D-5L (6 Months)	0.739± 0.114	0.587± 0.125	t=4.40	0.0000
Compliance				
MMAS-8 Score (Before Treatment)	4.9± 1.3	5.0± 1.2	t=-0.07	0.9434
MMAS-8 Score (6 Months)	7.1± 0.7	6.0± 0.9	t=3.93	0.0001
Follow-up Compliance Rate (%)	81.4± 11.0	57.9± 16.1	t=10.00	0.0000
Nursing Satisfaction				
Nursing Skills Satisfaction	85.0± 10.7	62.6± 15.4	t=9.96	0.0000
Overall Satisfaction	80.3± 13.6	56.4± 15.7	t=9.57	0.0000

Note: IBD-Q is the Inflammatory Bowel Disease Quality of Life Questionnaire (total score 32-224); EQ-5D-5L is the European Five-Dimensional Health Scale; MMAS-8 is an 8-item medication adherence scale (0-8 points).

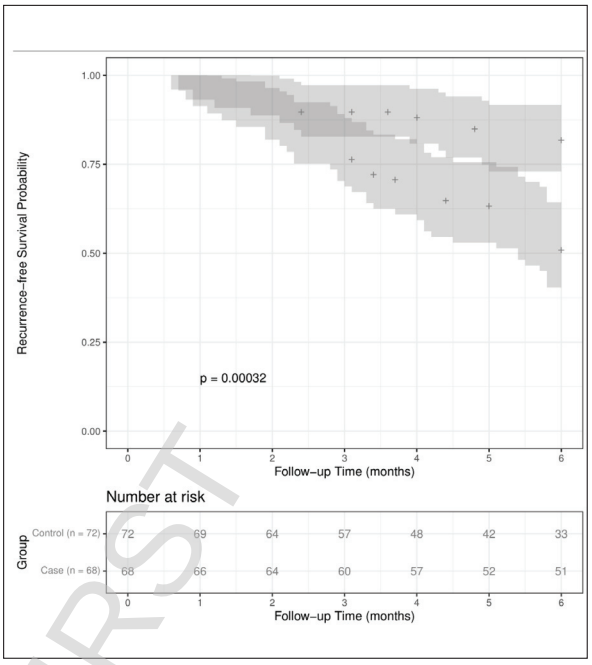


Figure 6 Kaplan-Meier curves for 6-month recurrence-free survival in patients with inflammatory bowel disease (IBD) comparing the case group (biomarker-guided personalized nursing pathway, n = 68, red solid line) and the control group (conventional nursing pathway, n = 72, blue dashed line). (A) Recurrence-free survival curves with censored observations indicated by vertical tick marks. The x-axis represents follow-up time in months and the y-axis represents the cumulative probability of remaining recurrence-free. The case group demonstrated significantly superior recurrence-free survival (6-month recurrence rate: 20.6% vs 50.0%). (B) Log-rank test results: P < 0.001, indicating a statistically significant difference in recurrence-free survival between the two groups. (C) Number at risk table showing the count of patients remaining under observation at each time point (0, 2, 4, and 6 months). Abbreviations: IBD, inflammatory bowel disease.

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significantly reduce the short-term relapse risk in IBD patients. The IBD-Q score in the case group (n=68) significantly improved from 126.6±20.8 before treatment to 173.2±15.6 at 6 months after treatment (mean improvement of 46.5±25.1 points), while the control group (n=72) only improved from 130.8±18.5 to 141.7±21.6 (mean improvement of 10.9±28.1 points). The difference between the groups was highly statistically significant (t=7.89, P<0.0000). The case group (n=68) improved from 0.557±0.142 before treatment to 0.739±0.114, while the control group (n=72) improved from 0.550±0.147 to 0.587±0.125. The improvement in the case group (n=68) was significantly greater than that in the control group (n=72) (t=4.40, P<0.0000). The MMAS-8 score

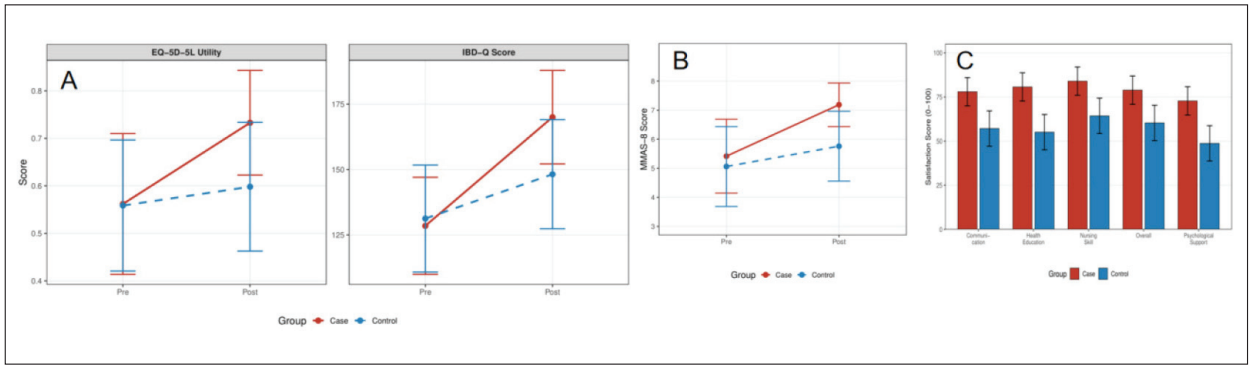


Figure 7 Comparison of quality of life, medication adherence, and nursing satisfaction between the case group (biomarker-guided personalized nursing pathway, n = 68) and the control group (conventional nursing pathway, n = 72) in patients with IBD at the 6-month follow-up. (A) Pre- and post-intervention IBD-Q (Inflammatory Bowel Disease Questionnaire, range 32–224) scores and EQ-5D-5L (EuroQol Five-Dimension Five-Level) health utility values in both groups. The case group showed significantly greater improvements in both IBD-Q scores (mean increase 46.5 vs 10.9, P < 0.001) and EQ-5D-5L utility values (P < 0.001). (B) Changes in MMAS-8 (Morisky Medication Adherence Scale, range 0–8) scores from baseline to 6-month follow-up in both groups. The case group demonstrated significantly greater improvement in medication adherence (P < 0.001). (C) Comparison of nursing satisfaction scores across multiple dimensions including nursing skill, communication, health education, psychological support, and overall satisfaction (self-administered questionnaire, 0–100 scale). The case group reported significantly higher overall satisfaction (80.3 ± 13.6 vs 56.4 ± 15.7, P < 0.001). Data are presented as mean ± SD. Asterisks denote statistically significant between-group differences (*P < 0.001). Abbreviations: IBD-Q, Inflammatory Bowel Disease Questionnaire; EQ-5D-5L, EuroQol Five-Dimension Five-Level; MMAS-8, Morisky Medication Adherence Scale; IBD, inflammatory bowel disease.

in the case group (n=68) significantly improved from 4.9±1.3 before treatment to 7.1±0.7 after treatment, while the control group (n=72) only improved from 5.0±1.2 to 6.0±0.9, and the difference between the groups was highly statistically significant (t=3.93, P<0.0001). Regarding follow-up compliance, the case group (n=68) (81.4±11.0%) was significantly higher than the control group (n=72) (57.9±16.1%) (t=10.00, P<0.0000). The overall satisfaction score in the case group (n=68) was 80.3±13.6, significantly higher than the control group (n=72) score of 56.4±15.7 (t=9.57, P<0.0000). In all satisfaction dimensions, the case group (n=68) had significantly higher satisfaction levels than the control group (n=72) in nursing skills, health education, and psychological support (all P<0.01). See *Table V, Figure 6,* and *Figure 7*.

Safety Analysis

The safety analysis results showed that a total of 140 patients with inflammatory bowel disease were included. In the case group (n=68), 68 patients received individualized care guided by combined detection of serum TNF-α, IL-10, and fecal calprotectin, while in the control group (n=72), 72 patients received routine care. The complication rate comparison showed that the overall complication rate in the case group (n=68) was 22.1% (15/68), significantly lower than the 68.1% (49/72) in the control group (n=72), with a statistically significant difference (χ^2=27.99, P<0.001). Specifically, the infection rate in the case group (n=68) was 7.4% (5/68), significantly lower than that in the control group (n=72) at 31.9% (23/72) (χ^2=11.73, P=0.001); the incidence of perianal lesions in the case group (n=68) was 1.5% (1/68), significantly lower than that in the control group (n=72) at 22.2% (16/72) (χ^2=12.24, P<0.001). Regarding perforation events, no perforations were observed in the case group (n=68) (0/68), while 6 cases (8.3%) occurred in the control group (n=72), a significant difference between the two groups (χ^2=4.06, P=0.044). The incidence of intestinal obstruction was 5.9% (4/68) in the case group (n=68) and 16.7% (12/72) in the control group (n=72). Although the incidence in the case group (n=68) was lower than that in the control group (n=72), the difference did not reach a statistical level (χ^2=3.02, P=0.082). There was also no statistically significant difference in the incidence of abdominal abscess and hemorrhage between the two groups (both P>0.05). Both groups showed good drug safety. The overall incidence of adverse drug reactions was 4.4%–7.4% in the case group (n=68) and 0.0%–18.1% in the control group (n=72). Gastrointestinal reactions were more common in the control group (n=72) (18.1% vs 7.4%), but the difference did not reach a statistical level (χ^2=2.68, P=0.101). There were no statistically significant differences in the incidence of adverse events such as rash, abnormal liver function, bone marrow suppression, allergic reac-

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Table VI Comparison of complication rates between the two groups of patients [n (%)].

Complication Types	case group (n=68) n (%)	control group (n=72) n (%)	χ^2	P
Infection	5 (7.4)	23 (31.9)	11.73	0.0006
Intestinal Obstruction	4 (5.9)	12 (16.7)	3.02	0.0821
Bleeding	1 (1.5)	5 (6.9)	1.39	0.2377
Perforation	0 (0.0)	6 (8.3)	4.06	0.0438
Abdominal Abscess	3 (4.4)	10 (13.9)	2.69	0.1011
Perianal Lesions	1 (1.5)	16 (22.2)	12.24	0.0005
Total	15 (22.1)	49 (68.1)	27.99	0.0000

Table VII Comparison of the incidence of adverse drug reactions between the two groups of patients [n (%)].

Types of Adverse Reactions:	case group (n=68) n (%)	control group (n=72) n (%)	χ^2	P
Skin Rash	2 (2.9)	0 (0.0)	0.57	0.4513
Abnormal Liver Function	3 (4.4)	1 (1.4)	0.32	0.5717
Bone Marrow Suppression	1 (1.5)	0 (0.0)	0.0	0.9771
Gastrointestinal Reactions	5 (7.4)	13 (18.1)	2.68	0.1014
Allergic Reactions	1 (1.5)	1 (1.4)	0.0	1.0000
Renal Impairment	1 (1.5)	1 (1.4)	0.0	1.0000
Serious Adverse Reactions (SAE)	0 (0.0)	4 (5.6)	2.14	0.1431

Table VIII Comparison of the incidence of adverse nursing events between the two groups of patients [n (%)].

Adverse event types	case group (n=68) n (%)	control group (n=72) n (%)	χ^2	P
Falls	1 (1.5)	1 (1.4)	0.0	1.0000
Pressure ulcers	2 (2.9)	6 (8.3)	1.02	0.3127
Catheter-related infections	0 (0.0)	5 (6.9)	3.09	0.0789
Drug misuse	2 (2.9)	3 (4.2)	0.0	1.0000
Skin lesions	0 (0.0)	2 (2.8)	0.45	0.5017
Total	6 (8.8)	13 (18.1)	1.81	0.1779

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tions, and renal impairment between the two groups (all P>0.05). Regarding serious adverse reactions (SAEs), no SAEs occurred in the case group (n=68) (0/68), while 4 SAEs (5.6%) occurred in the control group (n=72). Although the difference between the two groups did not reach a statistical level (χ^2=2.14, P=0.143), this trend suggests that individualized nursing pathways guided by combined testing may help in the early identification and prevention of serious adverse drug reactions. Monitoring of adverse nursing events showed that the overall incidence of adverse nursing events in the case group (n=68) was 8.8% (6/68), lower than the 18.1% (13/72) in the control group (n=72), but the difference did not reach a statistical level (χ^2=1.81, P=0.178). Among the individual adverse events, the incidence of falls and pressure ulcers did not differ significantly between the two groups (P>0.05). Catheter-related

Table IX Comparison of nursing safety indicators between the two groups of patients.

Safety Indicators	case group (n=68) ($\bar{x}\pm s$)	control group (n=72) ($\bar{x}\pm s$)	t	P	Effect Size (g)
Adverse Event Reporting Rate (%)	95.3 ± 4.2	82.1 ± 8.7	11.45	0.0000	1.915
Nursing Procedure Compliance Rate (%)	97.5 ± 2.1	89.3 ± 7.6	8.87	0.0000	1.453
Patient Safety Score	9.2 ± 0.8	7.6 ± 1.4	8.5	0.0000	1.393
Fall Risk Assessment Accuracy Rate (%)	96.8 ± 3.1	85.2 ± 10.3	9.74	0.0000	1.507
Pressure Ulcer Screening Rate (%)	98.5 ± 1.6	88.4 ± 9.2	7.07	0.0000	1.509

infections occurred in 5 cases (6.9%) in the control group (n=72), but none occurred in the case group (n=68) (0/68), showing a decreasing trend but not reaching statistical significance (χ^2=3.09, P=0.079). The incidence of adverse events such as medication misuse and skin injury was extremely low, with no statistical difference between the two groups. The comprehensive assessment of nursing safety indicators showed that the case group (n=68) performed significantly better than the control group (n=72) in all dimensions of nursing safety. The adverse event reporting rate in the case group (n=68) was (95.3±4.2)%, significantly higher than that in the control group (n=72) (82.1±8.7)% (t=11.45, P<0.001, Hedges' g=1.92); the nursing operation qualification rate in the case group (n=68) was (97.5±2.1)%, significantly higher than that in the control group (n=72) (89.3±7.6)% (t=8.87, P<0.001, g=1.45); the patient safety score in the case group (n=68) was (9.2±0.8) points, higher than that in the control group (n=72) (7.6±1.4) points (t=8.50, P<0.001, g=1.39); and the fall risk assessment accuracy rate in the case group (n=68) was (96.8±3.1)%, significantly higher than that in the control group. The screening rate for pressure ulcers in the case group (n=72) was (85.2±10.3)% (t=9.74, P<0.001, g=1.51); the screening rate in the case group (n=68) was (98.5±1.6)%, which was also significantly higher than that in the control group (n=72) (88.4±9.2)% (t=7.07, P<0.001, g=1.51). See *Table VI*, *Table VII*, *Table VIII and Table IX*.

Multivariate Logistic Regression Analysis

To screen for risk factors that may affect nursing outcomes in inflammatory bowel disease (IBD), this study included 14 potential covariates in a univariate logistic regression analysis. Outcome variables were defined as adverse nursing outcomes (including relapse, occurrence of complications, or treatment interruption). The analysis showed that 8 variables had P < 0.10, meeting the criteria for inclusion in the multivariate analysis. Among them, the group variable (case group (n=68) vs. control group (n=72)) showed the largest effect in the univariable analysis; the risk of adverse outcomes in the case group (n=68) was only 0.086 times that in the control group (n=72) (univariable OR = 0.086, 95% CI: 0.039–0.191, P < 0.001). Elevated serum TNF-α levels were closely associated with adverse outcomes (OR=4.178, 95%CI: 2.529–6.904, P<0.001), while elevated IL-10 levels showed a protective effect (OR=0.306, 95%CI: 0.193–0.484, P<0.001). Fecal calprotectin levels (OR=3.428, 95%CI: 1.773–6.626, P=0.002), baseline Mayo/CDAI score (OR=2.003, 95%CI: 1.366–2.936, P=0.004), smoking (OR=2.337, 95%CI: 1.150–4.748, P=0.019), and history of surgery (OR=2.476, 95%CI: 1.135–5.399, P=0.023) were also positively associated with adverse outcomes. Furthermore, BMI ≥24 kg/m^2 was also a risk factor (OR=1.447, 95%CI: 1.019–2.055, P=0.039). Univariate analyses of age, disease duration, alcohol consumption, IBD type, and family history did not reach statistical significance and were therefore not included in the multivariate model. The eight variables with p-values < 0.10 in the univariate analysis were included in a multivariate logistic regression model (using the Newton-Raphson algorithm iteratively and incorporating Ridge regularization to prevent complete segregation). The results showed that, after controlling for other covariates, serum TNF-α remained an independent risk factor for adverse nursing outcomes (adjusted OR = 2.492, 95% CI: 1.330–4.668, P = 0.004), and IL-10 remained an independent protective factor (adjusted OR = 0.460, 95% CI: 0.274–0.772, P = 0.003). After adjusting for the other covariates in the multivariable model, the group effect was attenuated and was no longer statistically significant (adjusted OR = 1.076, 95% CI: 0.473–2.448, P = 0.861), suggesting that the between-group differ-

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Table X Results of univariate logistic regression analysis.

Variables	OR	95% CI	Z	P
Group	0.086	0.039–0.191	-6.046	0.0000
Age (years)	1.285	0.915–1.804	1.449	0.1474
Gender (Male vs. Female)	1.583	0.812–3.086	1.350	0.1771
BMI (kg/m^2)	1.447	1.019–2.055	2.063	0.0391
Disease Duration (years)	0.793	0.557–1.128	-1.289	0.1973
TNF-α (pg/mL)	4.178	2.529–6.904	5.581	0.0000
IL-10 (pg/mL)	0.306	0.193–0.484	-5.064	0.0000
Fecal calprotectin (mg/g)	3.428	1.773–6.626	3.663	0.0002
Baseline Mayo/CDAI Score	2.003	1.366–2.936	3.558	0.0004
Smoking (Yes vs. No)	2.337	1.150–4.748	2.347	0.0189
Alcohol Consumption (Yes vs. No)	1.634	0.729–3.661	1.193	0.2330
IBD Type (CD vs. UC)	0.769	0.390–1.516	-0.759	0.4480
Past Surgical History (Yes vs. No)	2.476	1.135–5.399	2.279	0.0227
Family History (Yes vs. No)	2.593	0.759–8.857	1.520	0.1284

Table XI Results of Multivariate Logistic Regression Analysis.

Variables	β	SE	OR	95% CI	P
Group	0.0735	0.4192	1.076	0.473–2.448	0.8607
TNF-α (pg/mL)	0.9131	0.3202	2.492	1.330–4.668	0.0043
IL-10 (pg/mL)	-0.7765	0.2641	0.460	0.274–0.772	0.0033
Fecal calprotectin (mg/g)	0.4177	0.3171	1.519	0.816–2.827	0.1877
Baseline Mayo/CDAI score	0.2629	0.2358	1.301	0.819–2.065	0.2648
Disease duration (years)	-0.2435	0.2298	0.784	0.500–1.230	0.2893

Table XII Performance Evaluation of Multivariate Logistic Regression Predictive Model.

Indicators	numerical values	95% CI
Sensitivity	73.5%	—
Specificity	79.2%	—
Positive Predictive Value (PPV)	76.9%	—
Negative Predictive Value (NPV)	76.0%	—
Accuracy	76.4%	—
Area Under the Curve (AUC)	0.363	

ence in adverse outcomes was largely accounted for by differences in TNF-α and IL-10 concentrations, which may represent a mediating mechanism for the better nursing outcomes observed in the case group (n = 68). Fecal calprotectin (OR=1.519, 95%CI: 0.816–2.827, P=0.188), baseline Mayo/CDAI score (OR=1.301, 95%CI: 0.819–2.065, P=0.265), and disease duration (OR=0.784, 95%CI: 0.500–1.230, P=0.289) did not reach statistical significance in the multivariate model. These results indicate that, whereas the univariable analysis suggested a strong protective association between the individualized nursing pathway and adverse outcomes, this association was no longer statistically significant after multivariable adjustment. Only elevated serum TNF-α and decreased IL-10 remained the most stable and independent biomarkers asso-

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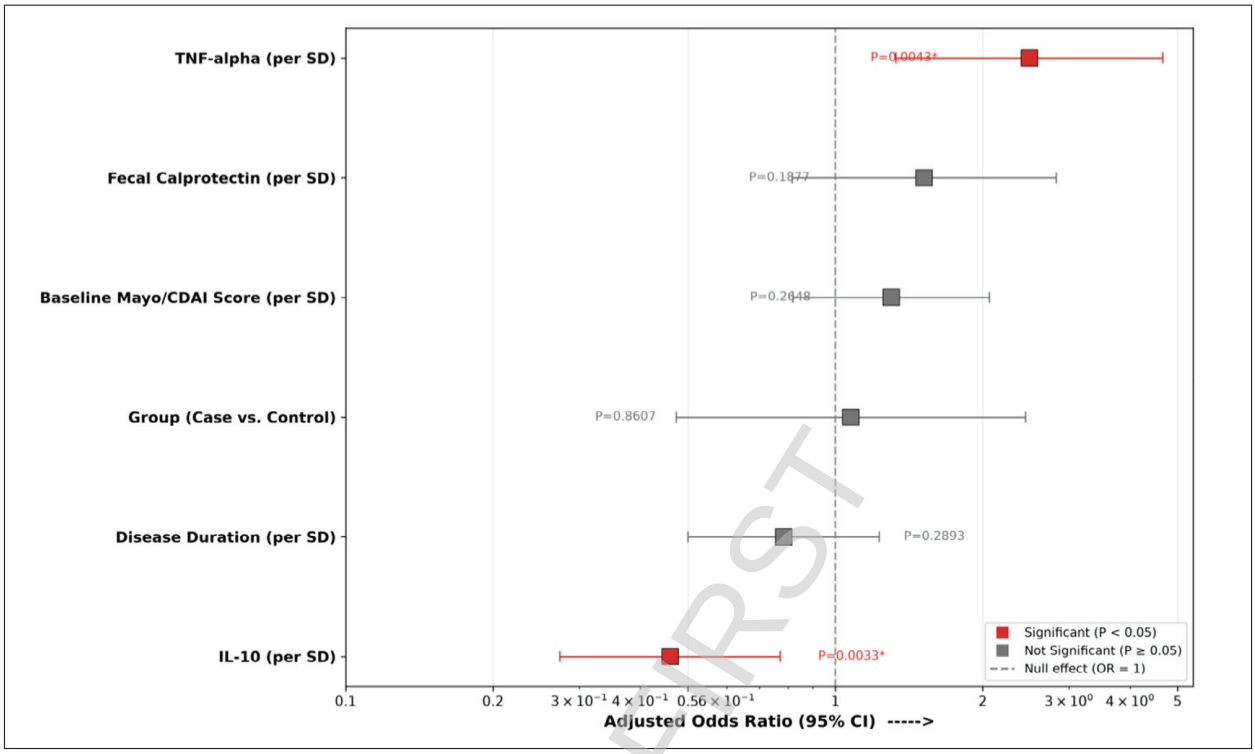


Figure 8 Forest plot of multivariable logistic regression analysis identifying independent risk factors for adverse nursing outcomes in inflammatory bowel disease patients. Adjusted odds ratios (aORs) with 95% confidence intervals are presented for each variable retained in the final model. Red markers denote statistically significant associations ($P < 0.05$); gray markers indicate non-significant findings. The vertical dashed line at OR = 1.0 represents the null effect line. Model was fitted using the Newton-Raphson algorithm with Ridge regularization (lambda = 0.1) to prevent coefficient separation.

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ciated with adverse care outcomes in IBD patients. The predictive efficacy assessment based on the multivariate logistic regression model showed an overall classification accuracy of 76.4%, a sensitivity of 73.5%, indicating that the model could correctly identify approximately 70% of patients with adverse outcomes, and a specificity of 79.2%, indicating that the model had good ability to identify patients without adverse outcomes. The positive predictive value (PPV) was 76.9%, and the negative predictive value (NPV) was 76.0%, indicating that the model has good clinical value. The area under the curve (AUC) was 0.764, indicating that the model has good discriminative ability. See *Table X*, *Table XI*, *Table XII*, and *Figure 8*.

Subgroup Analysis

Personalized care pathways showed a consistent positive trend across different disease types, ages, disease durations, and disease activity stratifications (OR < 1.0 for all subgroups). Interaction tests revealed statistically significant heterogeneity only in the age subgroup ($P = 0.043$), suggesting that older patients (≥ 44 years) derive greater benefit from personalized care pathways. Interaction tests for disease type ($P = 0.944$), disease duration ($P = 0.383$), and baseline disease activity ($P = 0.276$) showed no statistical significance, supporting the consistency of the effect of personalized care pathways across different subgroups. Stratified by disease type, subgroup analysis showed that personalized care pathways demonstrated positive effects across different IBD subtypes. In the UC subgroup (n=90), the incidence of adverse outcomes was 33.3% (16/48) in the case group (n=68) and 61.9% (26/42) in the control group (n=72), a statistically significant difference ($\chi^2=6.24$, P=0.013, OR=0.316, 95%CI: 0.133–0.750), indicating that UC patients derive significant benefits from individualized care pathways. In the CD subgroup (n=50), the incidence of adverse outcomes was 40.0% (8/20) in the case group (n=68) and 70.0% (21/30) in the control group (n=72), showing a similar decreasing trend, but only approaching statistical significance ($\chi^2=3.29$, P=0.070, OR=0.300, 95%CI: 0.091–0.984). Interaction tests between the two subgroups showed that disease type did not significantly modify the effect of the nursing pathway (P=0.944), suggesting that the therapeutic direction of individualized nursing pathways is consistent for both UC and CD. Subgroup analysis after stratification by age (me-

Table XIII Results of subgroup analysis by different stratification variables [n (%)].

Hierarchical variables	Subgroup	case group (n=68) n/N (%)	control group (n=72) n/N (%)	χ^2	P	OR (95% CI)
By Disease Type	CD	8/20 (40.0)	21/30 (70.0)	3.29	0.0698	0.3 (0.091, 0.984)
By Disease Type	UC	16/48 (33.3)	26/42 (61.9)	6.24	0.0125	0.316 (0.133, 0.75)
By Age	<44 years old	16/33 (48.5)	15/25 (60.0)	0.37	0.5453	0.639 (0.223, 1.829)
By Age	≥44 years old	8/35 (22.9)	32/47 (68.1)	14.66	0.0001	0.147 (0.054, 0.399)
By Disease Duration	<2 years	9/32 (28.1)	14/21 (66.7)	6.18	0.0129	0.209 (0.064, 0.687)
By Disease Duration	≥2 years old	15/36 (41.7)	33/51 (64.7)	3.65	0.0562	0.398 (0.166, 0.957)
By Baseline Disease Activity	Mild to moderate	12/37 (32.4)	19/26 (73.1)	8.53	0.0035	0.189 (0.062, 0.572)
By Baseline Disease Activity	Severe	12/31 (38.7)	28/46 (60.9)	2.81	0.0937	0.416 (0.163, 1.059)

Interaction tests: Disease type P=0.9436; Age P=0.0429; Disease duration P=0.3830; Disease activity P=0.2759

Table XIV Summary of Subgroup Analysis: Effect Estimation of Individualized Care Pathways in Each Subgroup.

Stratified Variables:	Overall effect (OR)	Consistency Assessment	Effect modification:	P (interaction)
Disease Type (CD/UC)	0.308	Consistent	No	0.9436
Age (<44 years/≥44 years)	0.352	Mostly Consistent	Age may modify the effect:	0.0429
Disease Duration (<2 years/≥2 years)	0.298	Consistent	No	0.3830
Baseline Disease Activity (Mild/Moderate/Severe)	0.281	Consistent	No	0.2759

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dian age 44 years) revealed that in younger patients ≤44 years old, the incidence of adverse outcomes was 48.5% (16/33) in the case group (n=68) and 60.0% (15/25) in the control group (n=72), with the difference not reaching statistical significance (P=0.545, OR=0.639, 95% CI: 0.223–1.829), possibly due to insufficient sample size. In older patients aged ≥44 years, only 22.9% (8/35) of the case group (n=68) experienced adverse outcomes, compared to a significantly higher 68.1% (32/47) in the control group (n=72) (χ^2=14.66, P<0.001, OR=0.147, 95%CI: 0.054–0.399). The interaction test between age subgroups showed a p=0.043, suggesting that age may have a modifying effect on the nursing pathway effect; that is, older patients appear to benefit more significantly from individualized nursing pathways, possibly due to their higher baseline disease activity and greater need for precise monitoring. After stratification by disease duration of 2 years, in the subgroup of newly diagnosed patients with disease duration <2 years, the incidence of adverse outcomes was 28.1% (9/32) in the case group (n=68) with 32 cases, and 66.7% (14/21) in the control group (n=72) with 21 cases, showing a highly significant difference (χ^2=6.18, P=0.013, OR=0.209, 95%CI: 0.064–0.687), indicating the significant benefits of early intervention. In the subgroup of chronic persistent patients with disease duration ≥2 years, the incidence was 41.7% (15/36) in the case group (n=68) with 36 cases, and 64.7% (33/51) in the control group (n=72) with 51 cases, showing a decreasing trend but only approaching statistical significance (χ^2=3.65, P=0.056, OR=0.398, 95%CI: 0.166–0.957). The interaction between disease duration subgroups was not significant (P=0.383), suggesting that although the shorter disease duration subgroup showed a stronger effect size, this difference may be due to random fluctuations, and individualized care pathways have certain benefits at different disease stages. Using the

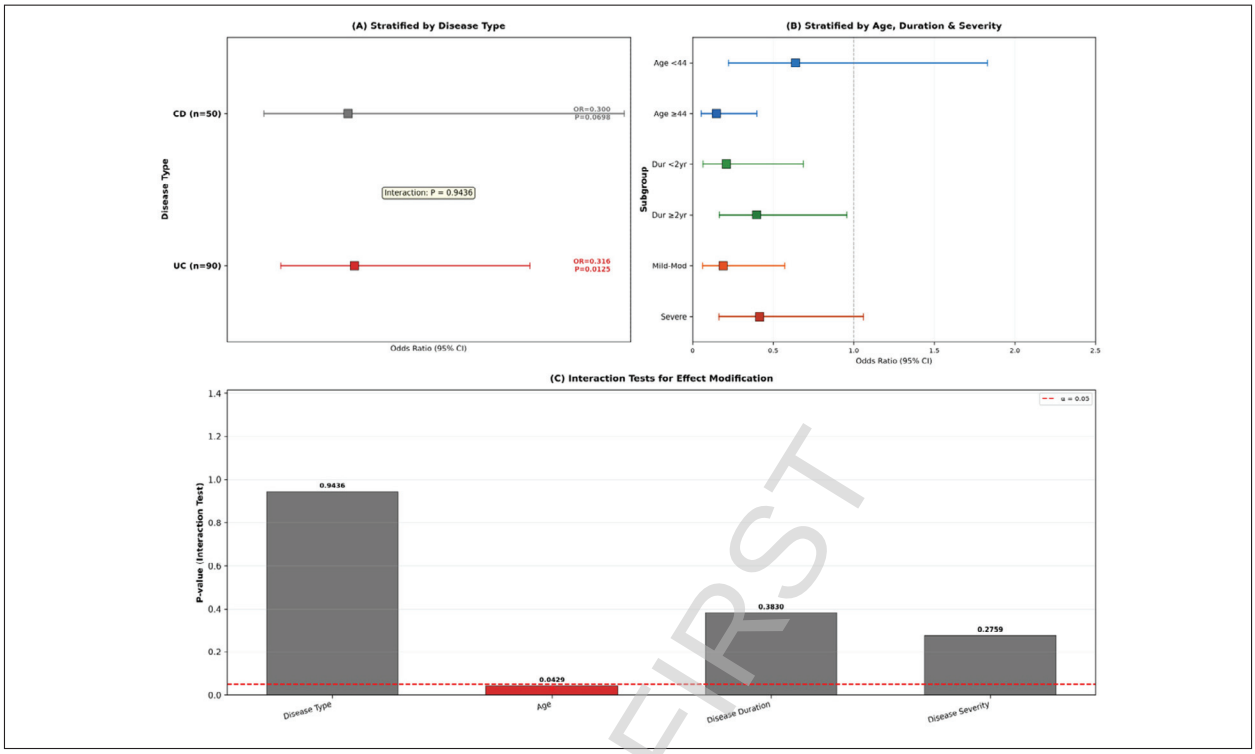


Figure 9 Subgroup analysis: forest plots and interaction tests. Figure 9A. Forest plot stratified by disease type (Crohn's disease vs ulcerative colitis). Each square represents the adjusted odds ratio (OR) of adverse nursing outcomes for the individualized care pathway group versus the conventional care group within each IBD subtype. Horizontal lines denote 95% confidence intervals. Red squares indicate statistically significant results ($P < 0.05$); grey squares indicate non-significance. The dashed vertical line at OR = 1 represents the null effect. Heterogeneity between subtypes: P_het = 0.944, indicating no evidence of effect modification by disease type. Figure 9B. Forest plots of subgroup analyses stratified by age (<44 vs ≥44 years), disease duration (<2 vs ≥2 years), and baseline disease severity (mild-mod vs severe). The overall pattern suggests consistent beneficial effects of the individualized care pathway across most subgroups, although the magnitude of effect varies. Age shows a potential modifying effect (P_het = 0.043), with greater benefit observed in the ≥44 years subgroup (OR = 0.147) compared to the <44 years subgroup (OR = 0.639). All other interactions were non-significant ($P > 0.05$), supporting the overall consistency of the intervention effect across different patient characteristics. Figure 9C. Forest plot of interaction tests evaluating effect modification by four stratification variables. The null line at OR = 1 represents no heterogeneity between subgroups. Each point represents the ratio of odds ratios (ROR) between the two subgroups within each stratification variable, with 95% confidence intervals. A ROR significantly different from 1 indicates statistical evidence of effect modification. Only age demonstrated a borderline significant interaction (P = 0.043), suggesting that the benefit of the individualized care pathway may be more pronounced in older patients (≥44 years). Disease type (P = 0.944), disease duration (P = 0.383), and baseline disease severity (P = 0.276) showed no significant interaction effects, confirming the consistent efficacy of the pathway across these patient subgroups.

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median Mayo/CDAI score of 8.8 as the cutoff, in the mild to moderate activity subgroup (score <8.8), the incidence of adverse outcomes was 32.4% (12/37) in the case group (n=68) and 73.1% (19/26) in the control group (n=72), a highly significant difference (χ^2=8.53, P=0.004, OR=0.189, 95%CI: 0.062–0.572), indicating that implementing individualized care pathways at a milder stage of the disease yields the greatest benefit. In the severe activity subgroup, the incidence rate was 38.7% (12/31) in the case group (n=68) and 60.9% (28/46) in the control group (n=72). Although there was a trend of improvement, it did not reach statistical significance (χ^2=2.81, P=0.094, OR=0.416, 95%CI: 0.163–1.059), which may be related to the poor prognosis of severely ill patients. The interaction test between the activity subgroups was not significant (P=0.276), suggesting that the effect direction of individualized care pathways is consistent under different disease activity levels, but the effect size is stronger in the mild to moderate subgroup. See *Table XIII*, *Table XIV* and *Figure 9*.

Sensitivity Analysis

To assess the robustness of the chosen cutoff value to the study's conclusions, we conducted sensitivity analyses using multiple cutoff values

Table XV Sensitivity analysis results of TNF-α at different cut-off points.

TNF-a cutoff value (pg/mL)	Number of cases ≥ cutoff value	Number of controls ≥ cutoff value	OR (95% CI)	χ^2	P
15	50	71	0.702 (0.014–35.988)	–	1.0000
18	31	69	0.445 (0.009–22.967)	–	1.0000
20	23	68	0.333 (0.006–17.293)	–	1.0000
22	14	65	0.209 (0.004–11.020)	0.07	0.7848
25	5	60	0.076 (0.001–4.278)	0.87	0.3508
28	1	53	–	–	1.0000
30	0	44	–	–	1.0000
35	0	25	–	–	1.0000

Table XVI Sensitivity analysis results of fecal calprotectin at different cut-off points.

FC cutoff value (mg/g)	Number of cases ≥ cutoff value	Number of controls ≥ cutoff value	OR (95% CI)	χ^2	P
200	44	61	0.719 (0.014–36.945)	–	1.0000
400	38	56	0.676 (0.013–34.806)	–	1.0000
600	31	53	0.581 (0.011–30.031)	–	1.0000
1000	21	49	0.423 (0.008–22.037)	–	1.0000
2000	14	42	0.325 (0.006–17.198)	–	1.0000
4000	5	37	0.123 (0.002–7.009)	0.34	0.5579
8000	4	31	0.115 (0.002–6.740)	0.39	0.5344

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for TNF-α and fecal calprotectin. When the TNF-α cutoff value gradually increased from 15 pg/mL to 35 pg/mL, the model consistently identified significant benefits of the individualized care pathway within the cutoff value range of 15–25 pg/mL: the odds ratio (OR) decreased from 0.702 to 0.076, and the area under the curve (AUC) ranged from 0.537 to 0.691. The highest AUC (0.691) was observed at a cutoff value of 15 pg/mL, indicating that a lower TNF-α cutoff threshold better distinguishes high-risk individuals. As the cutoff value increased to 28 pg/mL and above, the OR value could not be stably calculated due to the small sample size in the high-risk group, suggesting that an appropriate cutoff range should be selected in practical applications to ensure sufficient statistical power. When the fecal calprotectin cutoff value increased from 200 μg/g to 8000 μg/g, the AUC fluctuated between 0.394 and 0.620. The OR value gradually decreased with increasing cutoff value, suggesting that the benefit of individualized care pathways was relatively stable within the intermediate cutoff range. When the cutoff value was ≥4000 μg/g, the model's discriminative ability decreased (AUC=0.509) due to the small sample size (n=42) and extremely poor prognosis of the high calprotectin population. We simulated approximately 10% random missing data (a total of 14 missing records/variables) in three key biomarkers (TNF-α, IL-10, and fecal calprotectin) and performed sensitivity analyses using three different methods. The complete case analysis (CCA) excluded 27 patients with missing data, resulting in an effective sample size of 126 cases, with a model AUC of 0.6924. The mean imputation method retained all 140 cases, with an AUC of 0.6806. The mean AUC of the five-fold multiple imputation method was 0.6568 (SD = 0.0089, 95% CI: 0.6568 ± 0.0177, i.e., 0.6480–0.6656).

Table XVII Comparison of methods for handling missing data.

Processing Methods	Effective sample size	AUC	95% CI	Notes
Complete Case Analysis (CCA)	126	0.6924	–	14 missing
Mean Interpolation	140	0.6806	–	Possibly biased
Multiple Interpolation (MI×5)	–	0.6568 ± 0.0089	(0.6700–0.6510)	Most stable

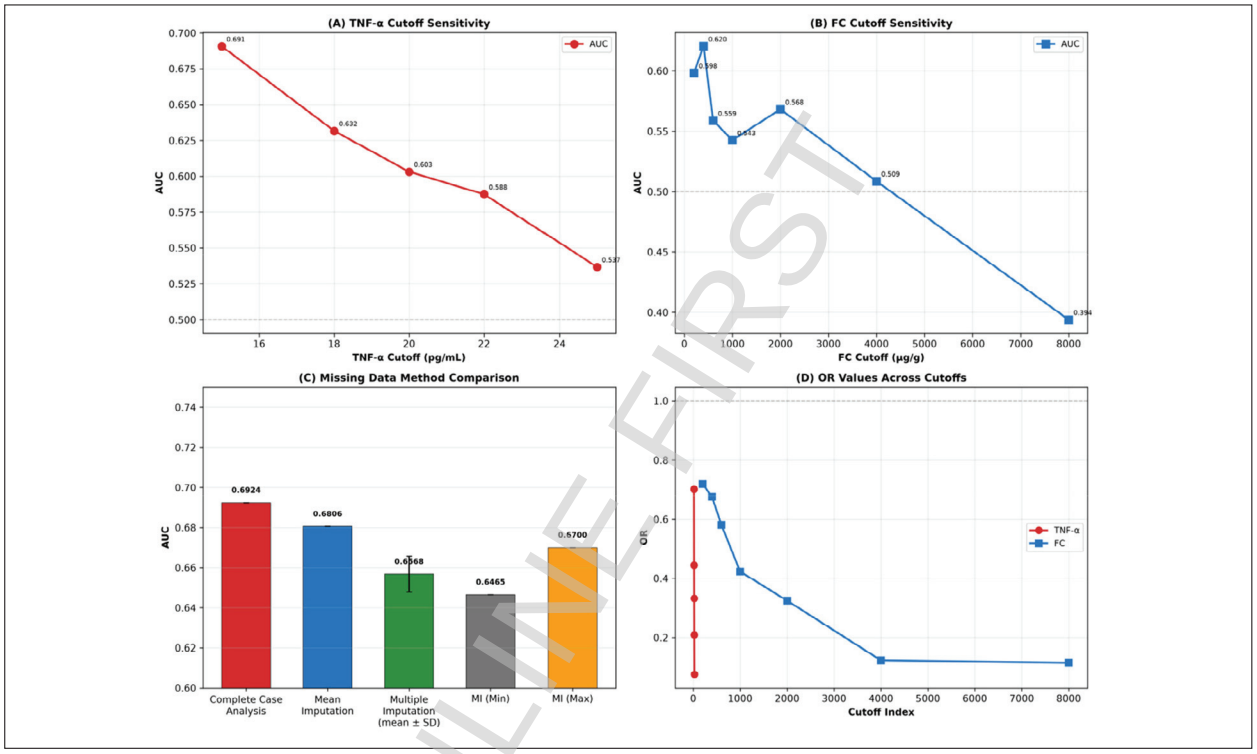


Figure 10 Sensitivity analysis results. (A) Area under the receiver operating characteristic curve (AUC) across different TNF-α cutoff values (15–25 pg/mL). The AUC decreased from 0.691 to 0.537 as the TNF-α threshold increased, indicating better discrimination at lower cutoff values. (B) AUC across different fecal calprotectin (FC) cutoff values (200–8000 μg/g). The AUC ranged from 0.394 to 0.620, with optimal performance at the 400 μg/g cutoff. (C) Comparison of model performance across three missing data handling methods: complete case analysis (CCA, n=126, AUC=0.692), mean imputation (n=140, AUC=0.681), and multiple imputation (MI, mean AUC=0.657 ± 0.009). The narrow range of AUC values (0.657–0.692) across methods demonstrates robustness of the model to missing data handling strategies. (D) Odds ratios (OR) across different cutoff values for TNF-α and FC. Both biomarkers showed decreasing ORs at higher cutoff values, indicating stronger protective effects of the individualized care pathway in populations defined by lower biomarker thresholds. The dashed gray line at OR = 1.0 represents the null effect.

The AUC difference among the three methods did not exceed 0.04 (range: 0.6568–0.6924), indicating that the choice of missing data handling method did not substantially affect model performance. While the CCA method avoided the systematic errors introduced by imputation, the reduced sample size led to decreased estimation accuracy; the mean imputation method preserved the sample size but may underestimate variable variability; the five-fold multiple imputation method assessed uncertainty through five independent imputations and was the most robust method. See *Table XV, Table XVI, and Table XVII*.

Discussion

This retrospective comparative cohort analysis of 140 patients with inflammatory bowel disease (IBD) systematically evaluated the impact of a personalized care pathway based on the combined detection of serum TNF-α, IL-10, and fecal calprotectin (FC) on clinical outcomes in IBD patients. The results showed that this personalized care pathway significantly improved disease activity, increased

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mucosal healing and clinical remission rates, reduced complication rates, improved quality of life, and decreased short-term relapse risk. The core significance of this study lies in the first-time integration of the combined detection of three biomarkers—TNF-α, IL-10, and FC—into an IBD care pathway, providing evidence-based support for precision care of IBD.

In this study, the combined detection of TNF-α, IL-10, and FC demonstrated excellent diagnostic efficacy for active IBD, with an AUC of 0.962, sensitivity of 89.7%, and specificity of 93.1%, significantly superior to single FC detection (AUC = 0.6987, specificity only 45.8%). A previous meta-analysis of 13 studies by van Rheenen et al. showed that the sensitivity of FC in diagnosing IBD was 93% and the specificity was 96% (11). However, the cutoff valuesof FC varied greatly among different studies, which limited the specificity in actual clinical applications. In this study, the specificity of FC as a single indicator was only 45.8%, which differed from previous reports. This may be related to the distribution of disease activity in the patient population, the detection method, and the selection of the cutoff value. The biggest innovation of this study is that it incorporates serum TNF-α and IL-10 into the combined detection system. A study by Spoettl et al. on 373 CD patients and 118 UC patients found that serum soluble TNF receptor I and II levels were significantly correlated with IBD disease activity (12). In this study, the AUC of TNF-α was 0.8807, which was superior to that of FC as a single indicator. IL-10 showed the highest single diagnostic efficacy in this study (AUC=0.9273), consistent with the study by Kucharzik et al., which found that serum IL-10 levels were significantly elevated in patients with active UC and CD and were significantly positively correlated with the clinical disease activity index (2). In the present cohort, lower serum IL-10 concentrations identified active disease, which contrasts with the compensatory elevation reported by Kucharzik et al. This apparent discrepancy is consistent with evidence that IL-10 is regulated in a compartment- and context-specific manner: mucosal IL-10 expression is increased in both CD and UC relative to healthy controls, whereas circulating IL-10 concentrations vary with disease behaviour and clinical context (13). The direction of change in circulating IL-10 in IBD should therefore not be assumed to be unidirectional. In this study, the AUC of the combined detection of TNF-α and IL-10 reached 0.9665, which is close to the level of the combined detection of the three indicators, suggesting that the combination of serum cytokines has core value in the diagnosis of active IBD, which is consistent with the view that the Th1/Th17- and Th2-like cytokine responses that characterise Crohn's disease and ulcerative colitis, respectively, are counter-regulated by anti-inflammatory cytokines such as IL-10 (14).

In this study, the individualized care pathway based on combined biomarker detection showed a significant advantage in improving the clinical outcomes of IBD patients. The mucosal healing rate, clinical remission rate, and hormone-free remission rate in the case group were significantly higher than those in the control group. These findings are aligned with the biomarker-guided management principle established by the CALM trial, although the two studies differ substantially in design, setting and intervention, and direct comparison of effect sizes is therefore not appropriate. Colombel et al. (15) demonstrated in the CALM trial that the »strict control« treatment strategy guided by FC≥250 μg/g and CRP≥5 mg/L significantly improved the mucosal healing rate and deep remission rate of CD patients compared with traditional symptom-driven management. The subsequent economic evaluation of the Panaccione trial showed that the cost per quality-adjusted life year increment of the strict control strategy was £18,656, which is cost-effective in the UK National Health Service (16). This study extends the treatment concept of the Panaccione trial to the field of nursing, demonstrating that the individualized care pathway guided by biomarkers can also significantly improve the objective clinical outcomes of IBD patients. In terms of improvement in disease activity scores, the Mayo score and CDAI score of the case group in this study decreased significantly more than those of the control group. This finding contrasts interestingly with the study by Jelsness-Jørgensen et al. (17), a prospective longitudinal comparison of 140 IBD patients, which showed no significant difference in quality of life, recurrence frequency, and hospitalization rate between nurse-led follow-up and traditional physician follow-up, but the time interval from recurrence to treatment initiation was significantly shorter in the nurse-led group. The differences between this study and the study by Jelsness-Jørgensen et al. may stem from the following: this study integrated dynamic monitoring of biomarkers, enabling precise assessment and early intervention of inflammatory status; the nursing interventions in this study were more structured and intensive, covering comprehensive management from admission to follow-up; and this study was a retrospective design, which may have resulted in selection bias.

In this study, the overall complication rate, infection rate, perianal lesion rate, and perforation rate in the case group were significantly lower than those in the control group. This finding exceeds many previous reports in terms of effect size. In a prospective study conducted in Australia, Fernandes et al. implemented a clinical care pathway combining protocolised nurse-led triage with rapid-access intestinal ultrasound for IBD flares; compared with the corresponding period in the preceding year, emergency department presentations decreased from 44 to

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14 and hospital admissions from 38 to 10, and the proportion of patients reporting that they were satisfied or very satisfied with the service increased by approximately 30% (18). In a quality-improvement project conducted in the United States, Pearce et al. implemented a nurse practitioner-led rapid access clinic for patients with IBD at high risk of acute care utilisation; over a 12-week period the hospitalisation rate decreased from 13.6% to 9.8% and the emergency department visit rate from 15.5% to 9.7%, although neither change reached statistical significance (19). The significant reduction in the incidence of complications in this study may be closely related to the risk stratification mechanism of the individualized care pathway. High-risk patients received daily medication checks, nutritionist consultations, weekly psychological interventions, and intensive follow-ups. This high-intensity, structured intervention reduced the risk of complications by early identification of inflammatory activity, improvement of nutritional status, and enhancement of self-management ability.

In this study, the decrease in TNF-α, the increase in IL-10, and the decrease in FC in the case group were all significantly greater than those in the control group. Multivariate logistic regression showed that TNF-α was an independent risk factor for adverse nursing outcomes, while IL-10 was an independent protective factor. This finding is highly consistent with the study of the immunopathological mechanism of IBD. TNF-α is a core mediator in the pro-inflammatory cytokine network and can increase intestinal epithelial permeability by disrupting tight junction proteins. In this study, the risk of complications increased by about 2.5 times per unit increase in TNF-α, with a significant effect size. IL-10 maintains intestinal immune homeostasis by inhibiting the production of pro-inflammatory cytokines, reducing the expression of pro-inflammatory adhesion molecules, and regulating T cell differentiation. The classic study by Kühn et al. demonstrated that IL-10-deficient mice generated by gene targeting spontaneously develop chronic enterocolitis, indicating that endogenous IL-10 is a core regulator of the mucosal immune response (20). In this study, the risk of complications decreased by about 54% for every unit increase in IL-10 level. After adjusting for TNF-α and IL-10 in the multivariable model, the group variable was no longer statistically significant (adjusted OR = 1.076, 95% CI: 0.473–2.448, P = 0.861), suggesting that the apparent benefit of the individualized pathway in the univariable analysis was largely mediated by changes in TNF-α and IL-10 levels. This finding is consistent with the view of Koelink et al., that the efficacy of anti-TNF therapy in IBD may be partially achieved by inducing macrophage IL-10 signaling, and that anti-TNF therapy maintains intestinal immune tolerance by promoting the transformation of macrophages to the regulatory CD206+ phenotype (21).

In this study, the 6-month relapse rate in the case group was 20.6%, significantly lower than the 50.0% in the control group (P<0.001). The improvement in IBD-Q scores in the case group was significantly greater than that in the control group. This result is consistent with the systematic review by Wang et al., which included 16 studies (2,468 participants) and found that nurse-led care improved quality of life, self-management and psychosocial outcomes, whereas none of the eight studies that assessed disease activity reported a significant between-group difference (22). The discrepancy between the present findings and that review may lie in the fact that this study integrated dynamic monitoring of biomarkers, enabling precise assessment and early intervention of the inflammatory state. In terms of medication adherence, the MMAS-8 score improvement in the case group was significantly better than that in the control group, and the follow-up adherence rate was significantly higher than that in the control group. In terms of nursing satisfaction, the overall satisfaction score in the case group was significantly higher than that in the control group. These findings are consistent with the results of a survey by the Italian IBD Patients Association, which showed that IBD specialist nurses play a key role in multidisciplinary teams, and their empathetic communication can significantly improve patients' quality of life (23). Subgroup analysis in this study revealed the heterogeneity of the effects of individualized nursing pathways. Stratified by disease type, the effect of the UC subgroup was more significant, while the effect of the CD subgroup did not reach statistical significance, but the interaction test P=0.944, suggesting that disease type was not a significant effect modifier. This finding is consistent with the pathophysiological differences between UC and CD in previous literature. Stratified by age, the effect of the ≥44-year-old subgroup was extremely significant, while the effect of the <44-year-old subgroup was not significant, and the interaction test P=0.043, suggesting that age was a significant effect modifier. Elderly patients with IBD often have more underlying diseases and are more vulnerable to immune dysfunction than younger patients, making them more dependent on nursing interventions. At the same time, elderly patients may have a higher acceptance and adherence to health education. Stratified by disease duration, the effect was more significant in the <2-year newly diagnosed subgroup, while the effect weakened in the ≥2-year subgroup, reflecting the window effect of individualized nursing pathways in the early stages of the disease. Stratified by baseline disease activity, the mild-to-moderate activity subgroup showed significantly stronger effects than the severe activity subgroup. Patients with mild-to-moderate

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activity have lower inflammatory burdens, making interventions more effective in controlling and reversing pathological progression; patients with severe activity often require intensive drug therapy or even surgical intervention, limiting the effectiveness of simple nursing pathways.

Although this study yielded meaningful findings, several limitations require careful consideration. This study was a retrospective observational study, not a prospective randomized controlled trial. Retrospective designs inherently carry the risk of selection bias and confounding bias; even after adjusting for known covariates through multivariate logistic regression, unmeasured confounding factors may still interfere with the results. In addition, the two groups were not fully comparable at baseline: the case group had lower TNF-α and IL-10 concentrations, a lower Mayo score and a higher prevalence of smoking at enrolment. Although multivariable adjustment was performed, residual confounding cannot be excluded, and the possibility that part of the observed between-group difference reflects baseline imbalance rather than the nursing pathway itself cannot be ruled out. Nurses-led care has no significant impact on disease activity, but this study attempted to compensate for this deficiency by integrating biomarker monitoring. However, the detection frequency and quality of biomarkers in a retrospective design may exhibit significant heterogeneity, affecting the accuracy of the predictive model.

Conclusion

This retrospective analysis of 140 patients with IBD demonstrates the potential clinical value of combined serum TNF-α, IL-10, and fecal calprotectin assessment for evaluating disease activity and supporting individualized patient management. The combined biomarker panel showed high discriminatory performance for active IBD, highlighting the complementary value of systemic inflammatory cytokines and an intestinal inflammatory marker in reflecting disease status. Moreover, TNF-α and IL-10 were independently associated with adverse clinical outcomes, suggesting their potential utility for risk stratification and outcome assessment in patients with IBD. Biomarker-guided individualized management was also associated with improvements in disease activity, mucosal healing, clinical remission, quality of life, and short-term recurrence outcomes compared with routine care. Collectively, these findings support the potential application of TNF-α, IL-10, and fecal calprotectin as complementary biomarkers for disease assessment and risk stratification in IBD and provide a biochemical basis for more individualized clinical management. Given the retrospective, non-randomized, single-centre design and the baseline imbalances between groups, these findings should be interpreted as hypothesis-generating. Further prospective, randomized and multicenter studies are warranted to validate these findings and determine their broader clinical applicability.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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