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Correlation Analysis of Empirical Dietary Inflammatory Index with Disease Severity and Systemic Inflammatory Status in Patients with Anal Fistula: A Multicenter Cross-Sectional Study

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Abstract

Objective

To investigate the correlation between the Empirical Dietary Inflammatory Index (eDII) and disease severity as well as systemic inflammatory status in patients with anal fistula, and to provide a scientific basis for clinical dietary interventions.

Methods

This multicenter cross-sectional study enrolled 50 patients with anal fistula (29 males and 21 females; mean age, 36.96 ± 11.12 years) who were admitted to the Affiliated Traditional Chinese Medicine Hospital of Guangzhou Medical University and the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from September 2024 to September 2025. Within 24 h of admission, all patients completed a validated food frequency questionnaire (FFQ) to assess their dietary intake in the month before disease onset, and the eDII was calculated accordingly. Fasting venous blood was collected on the day of the FFQ survey to detect systemic inflammatory markers, including white blood cell (WBC) count and C-reactive protein (CRP) level. The Shapiro–Wilk test was used to evaluate data normality. Spearman correlation analysis was performed to assess the bivariate correlation between the eDII and inflammatory markers. Regression analysis was performed to explore the association between the eDII and inflammatory markers. Kruskal–Wallis H test and Mann–Whitney U test with Dunn–Bonferroni post-hoc correction were used for intergroup comparison of disease severity subgroups.

Results

The mean eDII of the patients was 1.54 ± 2.10; the median WBC count was 7.09 × 10^9/L; and the median CRP level was 6.725 mg/L. In the normality test, the eDII showed a normal distribution ($p > 0.05$), while the WBC count and CRP level did not show a normal distribution (all $p < 0.05$). Spearman correlation analysis revealed that the eDII showed a significant positive correlation with the WBC count ($r = 0.464$, $p < 0.01$) and CRP level ($r = 0.842$, $p < 0.01$). Linear regression analysis indicated that the eDII had a significant positive effect on the WBC count and CRP level (both $p < 0.01$). Subgroup analysis revealed that the eDII, WBC counts, and CRP levels in the supra-sphincteric, complex, and high anal fistula groups were significantly higher than those observed in the corresponding mild disease groups (all $p < 0.05$) according to the Parks Classification, simple/complex classification, and high/low anal fistula classification, respectively.

Conclusion

A high eDII was independently and positively associated with a higher systemic inflammatory burden and greater disease severity in patients with anal fistula. Pro-inflammatory dietary patterns reflected by high eDII may be a potential influencing factor for disease progression. Dietary adjustment to reduce the eDII may be an

auxiliary strategy for improving inflammatory status, but its effect on prognosis needs to be verified by high-quality prospective studies.

Clinical Trial Registration

This study is a multicenter observational cross-sectional study, which does not fall into the category of interventional clinical trials that require mandatory registration under the International Committee of Medical Journal Editors (ICMJE) requirements. Thus, clinical trial registration is not applicable for this study.

Highlights

This is the first multicenter cross-sectional study to explore the correlation between the empirical dietary inflammatory index (eDII) and disease severity as well as systemic inflammatory status in patients with anal fistula.

The eDII is significantly positively correlated with white blood cell (WBC) count and C-reactive protein (CRP) level, the core systemic inflammatory markers, in anal fistula patients.

Higher eDII is independently and positively associated with greater anatomical complexity and severity of anal fistula verified by multiple clinical classification systems.

Dietary adjustment to reduce the eDII may serve as a potential auxiliary strategy for improving the systemic inflammatory status of patients with anal fistula.

1. Introduction

Anal fistula, one of the common and refractory diseases in anorectal surgery, is a chronic infectious disease of the perianal region that usually occurs secondary to rupture or incision drainage of acute perianal abscesses and is characterized by recurrent infection, poor healing, and a high recurrence rate. The incidence of anal fistula is approximately 2%, and it affects individuals of all age groups, with the peak incidence concentrated in those aged 20–40 years [1–3]. In China, the incidence in males is up to 2-3-fold higher than that in females [4]. Recurrent perianal infection and persistent inflammatory response are the core mechanisms leading to fistula non-healing, postoperative recurrence, and disease progression. An uncontrolled local inflammatory response can even progress to systemic infections such as septicemia, seriously affecting patients' quality of life and their physical and mental health [5–6].

Modern medical research has shown that the inflammatory response plays a core role in the course of anal fistula. Reducing the inflammatory response of the wound and promoting the smooth transition from the inflammatory phase to the granulation filling phase are of importance for accelerating the healing of postoperative wounds in patients with anal fistula. Existing studies have indicated [7] that the levels of interleukin (IL)-1 and tumor necrosis factor (TNF)-α increase significantly during wound healing. TNF-α is an important cytokine involved in the inflammatory response. A large number of studies have shown [8–9] that a persistent increase in the TNF-α level in wound secretions leads to cell apoptosis and necrosis due to

hyperosmotic stress, continuous cell cycle arrest, and induced inflammatory response of the wound, thereby delaying wound healing. IL-1β has a damaging effect on tissue cells, and it induces the release of other inflammatory mediators such as IL-6, producing a cascade effect [10]. TNF-α, which initiates a multidirectional inflammatory response and inflammation through mechanisms such as increasing the synthesis and release of factors by endothelial cells, similarly increases the synthesis and secretion of IL-6, also resulting in a cascade effect [11]. Therefore, detecting the expression of IL-6 is an essential step to reflect the inflammatory microenvironment of the wound. As the most commonly used and clinically accessible systemic inflammatory markers, the WBC count and CRP level can effectively reflect the overall inflammatory burden of patients with anal fistula, and are closely related to disease severity and postoperative prognosis.

The role of dietary factors in inflammation regulation has attracted extensive attention. The Dietary Inflammatory Index (DII) [12] is a validated tool to evaluate the association between dietary patterns and inflammatory indicators based on 18 food groups, of which nine are anti-inflammatory food groups and nine are pro-inflammatory food groups, and the levels of three plasma inflammatory markers (IL-6, CRP, TNF-α receptor 2 [TNFαR2]). Ultimately, a higher DII indicates a higher intake of pro-inflammatory food groups, i.e., a pro-inflammatory dietary pattern, and vice versa for an anti-inflammatory dietary pattern. In 2019, Japanese scholars developed a new Empirical DII (eDII) based on the DII, which reflects the inflammatory potential of diet by analyzing the association between the food group intake frequency and the incidence of inflammatory aging-related inflammatory diseases. The eDII is simpler to calculate, and the research results are more easily translated into health-promoting dietary recommendations [13]. Previous studies have shown that a high eDII value is associated with an increased risk of various chronic diseases, elevated levels of inflammatory factors, and poor prognosis [14–15]. However, no studies to date have reported the correlation between the eDII and disease severity as well as inflammatory status in patients with anal fistula, and the role of dietary inflammatory potential in the progression of anal fistula remains unclear. We hypothesized that a pro-inflammatory dietary pattern reflected by a higher eDII is associated with a higher systemic inflammatory burden (elevated WBC and CRP levels) and more severe disease (higher Parks Classification grade, complex fistula, and high anal fistula) in patients with anal fistula. This study is the first to systematically verify this hypothesis with multicenter clinical data, with the aim of providing a scientific basis for clinical dietary interventions in patients with anal fistula and providing a new perspective for exploring the factors influencing anal fistula progression.

2. Materials and Methods

2.1 Study Participants

2.1.1 Study Design

This multicenter cross-sectional study, which aimed to investigate the correlation between the eDII and disease severity as well as inflammatory status in patients with anal fistula, was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine

2.1.2 Inclusion Criteria

A total of 50 patients with anal fistula admitted to the Affiliated Traditional Chinese Medicine Hospital of Guangzhou Medical University and the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from September 2024 to October 2025 were consecutively enrolled in this study. The inclusion criteria were as follows: met the diagnostic criteria for anal fistula in the 2022 *Clinical Practice Guidelines for Perianal Abscess, Fistula-in-Ano, and Rectovaginal Fistula* issued by the American Society of Colon and Rectal Surgeons [16]; aged 18 to 75 years; admitted to the hospital for elective surgery, without surgical treatment or systemic antibiotic therapy within 72 h before admission; completed all questionnaire surveys and clinical examinations; provided written informed consent voluntarily and cooperated with the study procedures.

2.1.3 Exclusion Criteria

The exclusion criteria were as follows: patients with malignant tumors, severe cardiovascular diseases, uncontrolled diabetes mellitus, or other chronic diseases that may affect systemic inflammatory status; patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis), anal fissure, hemorrhoids, or other perianal diseases that may affect perianal inflammatory status; patients who received systemic glucocorticoid or immunosuppressive therapy within 3 months before admission; patients with acute infectious diseases in other parts of the body within 2 weeks before admission; and patients with incomplete clinical data or inability to cooperate to complete the questionnaire survey.

2.2 Data Collection Methods

All data were collected within 24 h of patient admission, and the specific contents were as follows: general clinical data, including age, sex, height, weight, body mass index (BMI), and previous perianal surgery history; dietary intake data, which was collected using a food frequency questionnaire (FFQ) to calculate the eDII; laboratory examination data obtained with fasting venous blood samples, including WBC count and CRP level; disease severity assessment data, including preoperative pelvic magnetic resonance imaging (MRI) results and intraoperative exploration records for fistula classification.

2.3 Calculation Method of eDII

The eDII was calculated using a validated food frequency questionnaire (FFQ) adapted for the Chinese population, which has been previously described and validated in a national multicenter study [17]. This FFQ investigated the intake frequency of 16 food groups over the month before the onset of anal fistula and categorized the intake as follows: never, < 1 time/week, 1–2 times/week, 3–4 times/week, 5–6 times/week, and ≥ 7 times/week. The scoring framework was formulated with reference to the original eDII development study by Kanauchi et al. [13], including eight pro-inflammatory food components (red meat, processed meat, refined grains, fried food, sugary beverages, solid fats, snacks, alcohol) and eight anti-inflammatory food components (vegetables, fruits, whole grains, legumes, nuts, fish, tea, and coffee). Each pro-inflammatory component was scored 0, 1, or 2 points (higher intake frequency to a higher score), and each anti-inflammatory component was scored 0, -1, or -2 points (higher intake frequency to a lower score).

For alcohol intake, the intake was converted to grams of ethanol per day (g/d) considering 500 mL per bottle of beer (alcohol content, 3.5%; 14 g ethanol per bottle). The scoring was assigned on the basis of a dose-response meta-analysis: 0 points for ethanol intake < 70 g/week (< 5 bottles/week) or ≥ 196 g/week (≥ 14 bottles/week), 1 point for 70–84 g/week (5–6 bottles/week), and 2 points for 98–182 g/week (7–13

bottles/week). The 0-point assignment for intake ≥ 14 bottles/week was consistent with the plateau of inflammatory correlation reported in the original eDII development study.

The total eDII ranged from − 16 to + 16, with higher scores indicating stronger pro-inflammatory potential of the dietary pattern. All FFQ surveys were conducted by uniformly trained researchers to ensure data consistency and reduce interview bias.

2.4 Detection of Inflammatory Markers

Fasting venous blood (5 mL) was collected from all patients on the early morning of the second day of admission. CRP levels were measured using an enzyme-linked immunosorbent assay (ELISA) after centrifugation, while the WBC count was determined by an automatic blood cell analyzer.

2.5 Disease Assessment

The disease severity of the patients was assessed using three classification systems based on preoperative pelvic MRI and intraoperative exploration records, namely, the Parks Classification, simple/complex anal fistula classification, and low/high anal fistula classification. The Parks Classification categorizes disease severity into four levels on the basis of the anatomical relationship between the course of the fistula tract and the anal sphincter complex, namely, inter-sphincteric fistula with a tract coursing between the internal and external anal sphincters, trans-sphincteric fistula with a tract penetrating the external anal sphincter and involving the ischiorectal fossa, supra-sphincteric fistula with a tract extending cephalad across the levator ani muscle and bypassing the deep part of the external anal sphincter, and extra-sphincteric fistula with a tract that does not pass through the anal sphincter complex at all. The simple/complex anal fistula classification was formulated on the basis of the number of fistula tracts, the course of branching tracts, comorbidities and underlying diseases, wherein a simple anal fistula was defined as a single, unbranched primary fistula tract with its internal opening located at the anal crypt, while a complex anal fistula was defined by the presence of multiple fistula tracts, multiple branching fistulous tracts, or concomitant Crohn’s disease, anal dysfunction, and other related conditions. The low/high anal fistula classification was determined by the anatomical relationship between the course of the fistula tract and the deep part of the external anal sphincter, with a low anal fistula showing a tract coursing entirely below the deep part of the external anal sphincter, and a high anal fistula showing a tract that involved or completely crossed the deep part of the external anal sphincter with a deep anatomical location. All classifications were completed independently by two attending colorectal surgeons with more than 5 years of clinical experience. The evaluators were blinded to the patients' eDII values and inflammatory marker levels.

2.6 Statistical Analysis

SPSS 27.0 software was used for statistical analysis. Shapiro–Wilk test was used to evaluate the normality of continuous data. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and non-normally distributed data were expressed as median (interquartile range, IQR). Spearman correlation analysis was used to evaluate the correlation between the eDII and inflammatory markers. Linear regression analysis was used to explore the effect of the eDII on the WBC count and CRP level. Linear regression analysis was performed to explore the independent effects of the eDII on the WBC count. The WBC count was subjected to logarithmic transformation to fit the normal distribution assumption, and a linear regression model was

constructed with the transformed ln (WBC) set as the dependent variable and the eDII as the core independent variable. Neither the original nor the log-transformed data of CRP levels conformed to the normal distribution, with significant overdispersion characteristics; therefore, negative binomial regression analysis was adopted. To meet the requirement of negative binomial regression for an integer-type dependent variable, the original CRP values were multiplied by 100 and rounded to the nearest integer (denoted as CRP × 100). A negative binomial regression model was subsequently established with the eDII as the core independent variable and the transformed CRP values as the dependent variable, to verify the independent correlation between the eDII and CRP level.

Intergroup comparisons of eDII scores, WBC counts, and CRP levels were conducted among subgroups stratified by disease severity. For data conforming to a normal distribution with homogeneity of variance, one-way analysis of variance (ANOVA) was used for multi-group comparisons, and an independent-samples *t*-test was applied for two-group comparisons. For non-normally distributed data, the Kruskal–Wallis test was performed for multi-group comparisons, followed by post-hoc Dunn's test with Bonferroni correction; the Mann–Whitney U test was adopted for two-group comparisons, with post-hoc Dunn's correction performed accordingly. In addition, η^2 (eta-squared) was calculated to evaluate the effect size of differences among multiple groups, and Cliff's delta was derived from nonparametric tests to assess the effect size of differences between two groups, so as to clarify the clinical significance of the observed intergroup differences.

3. Results

3.1 Comparison of General Data

A total of 50 clinically diagnosed patients with anal fistula treated at the Affiliated Hospital of Traditional Chinese Medicine of Guangzhou Medical University and the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from September 2024 to September 2025 were enrolled in this study, including 29 males and 21 females with a mean age of 36.96 ± 11.12 years, mean height of 1.67 ± 0.09 m, mean body weight of 70.79 ± 14.76 kg, and mean BMI of 25.189 ± 3.869 kg/m².

3.2 eDII, Levels of Inflammatory Markers, and Normality Test

The mean eDII of the 50 patients was 1.54 ± 2.10; the median WBC count was 7.09 × 10^9/L; and the median CRP level was 6.725 mg/L. Normality tests were performed for the eDII (dietary index), WBC count, and CRP levels. Since the sample size was ≤ 50, the Shapiro–Wilk test was used. The results presented in Table 1 indicate that the eDII showed no significant deviation from a normal distribution ($p > 0.05$), while the WBC count and CRP showed significant differences ($p < 0.05$), which did not conform to the normal distribution (Figs. 1–2).

Table 1
Normality test results for the eDII score and inflammatory markers (n = 50)

Name	Sample Size	Mean	Standard Deviation	Kolmogorov–Smirnov Test		Shapiro–Wilk Test	
				Statistic *D*	*p*	Statistic *W*	*p*
eDII	50	1.54	2.10	0.12	0.06	0.96	0.08
WBC	50	8.4	3.31	0.19	$p < 0.01$	0.887	$p < 0.01$
CRP	50	16.53	23.65	0.27	$p < 0.01$	0.678	$p < 0.01$

Figure 1. Normal Q-Q Plot of the white blood cell (WBC) count

Note: The Q-Q plot shows that the observed values of the WBC count deviated significantly from the expected normal distribution line, indicating that the WBC count does not follow a normal distribution.

Figure 2. Normal Q-Q Plot of the C-reactive protein (CRP) level

Note: The Q-Q plot shows that the observed values of the CRP level deviated significantly from the expected normal distribution line, indicating that the CRP level does not follow a normal distribution.

3.3 Correlation Analysis between the eDII and Inflammatory Markers

Spearman correlation analysis was used to analyze the correlations between the eDII and the WBC count and CRP levels. The results (Table 2) showed that the correlation coefficient between the eDII and the WBC count was 0.464, and that between the eDII and the CRP level was 0.842, with $p < 0.01$ for both, suggesting that the eDII was significantly positively correlated with these two inflammatory markers.

Table 2
Spearman correlation analysis between the eDII and inflammatory markers (n = 50)

	WBC			CRP		
	Correlation Coefficient	*p*	Sample Size	Correlation Coefficient	*p*	Sample Size
eDII	0.464	$p < 0.01$	50	0.842	$p < 0.01$	50

3.4 Regression Analysis of eDII on Inflammatory Markers

The WBC count was subjected to logarithmic transformation to fit a normal distribution. Linear regression analysis was performed with the eDII as the independent variable and the log-transformed WBC count as the dependent variable. The results (Table 3) showed that the R^2 was 0.230, F was 14.373, $p < 0.01$, and the regression coefficient of eDII was 0.082, with $t = 3.791$ and $p < 0.01$ at this time, indicating that the eDII had a significant positive effect on the log-transformed WBC count.

The original data for the CRP level showed a non-normal distribution. After logarithmic transformation, the results of the Shapiro–Wilk test (W = 0.920, $P < 0.01$) indicated that the transformed data still did not conform to a normal distribution. Meanwhile, the CRP data were non-negative continuous values with significant overdispersion characteristics, which could not meet the model assumptions of linear regression. Therefore, negative binomial regression analysis was selected for this indicator. To facilitate negative binomial regression for integer-dependent variables, the original CRP value was amplified 100 times and rounded to the nearest integer (CRP × 100) as the final dependent variable. The eDII was set as the core independent variable, with the same confounding factors mentioned above adjusted in the model, to verify the independent correlation between the eDII and the CRP level. In the negative binomial regression analysis, the regression coefficient of the eDII was 1.462 with $p < 0.01$, indicating that the eDII exerts a significant positive effect on the converted dependent variable (CRP × 100).

Table 3
Linear Regression Analysis Results of ln WBC (n = 50)

	Unstandardized Coefficient		**Standardized Coefficient**	***t***	***p***	**95% Confidence interval**	**Collinearity Diagnosis**	
	B	**Standard Error**	***Beta***				**Variance inflation factor**	**Tolerance**
Constant	1.934	0.056	-	34.363	$p < 0.01$	1.821 ~ 2.048	-	-
eDII	0.082	0.022	0.480	3.791	$p < 0.01$	0.039 ~ 0.126	1.000	1.000
R^2	0.230							
Adjusted R^2	0.214							
F	F (1,48) = 14.373, $p = 0.000$							
D-W Value	1.673							
Note: Dependent variable = ln WBC								

Table 4
Summary of Negative Binomial Regression Analysis Results (n = 50)

Term	**Regression Coefficient**	**Standard Error**	***z*-value**	***p*-value**	**OR**	**95% CI for OR**
Intercept	6.608	0.142	46.645	$p < 0.01$	741.058	561.391 ~ 978.226
eDII	1.462	0.143	10.197	$p < 0.01$	4.314	3.257 ~ 5.714
Note: Dependent variable = CRP*100						
McFadden *R*-squared = 0.095						

3.5 Comparison of eDII and Inflammatory Markers in Different Disease Groups

3.5.1 Grouping by Parks Classification

One-way ANOVA (Table 5) showed significant differences in the eDII among different Parks classification groups ($P < 0.05$), with a “supra-sphincteric fistula group > trans-sphincteric fistula group > inter-sphincteric fistula group” trend. The results of the Kruskal–Wallis test (Table 6) showed a statistically significant difference in CRP levels among the different Parks Classification groups ($H = 10.139$, $P < 0.05$). Meanwhile, the η^2 (eta-squared) value was approximately 0.173, which corresponds to a large effect size according to Cohen's statistical convention, indicating that the between-group difference was not only statistically significant, but also of important clinical value. Pairwise comparisons with Dunn–Bonferroni correction revealed (Table 7) that CRP levels also showed a “supra-sphincteric fistula group > trans-sphincteric fistula group > inter-sphincteric fistula group” trend. In contrast, WBC counts showed no statistically significant differences in the different Parks Classification groups ($H = 1.042$, $P = 0.594$).

3.5.2 Grouping by the Number of Fistula Tracts

The results (Table 8) showed significant differences in the eDII between patients with simple and complex fistulas ($P < 0.05$). The eDII of patients with complex fistula was significantly higher than that of patients with simple fistula. The Mann–Whitney U test (Table 9) showed statistically significant differences in both CRP levels and WBC counts between the two groups. Specifically, both CRP levels ($U = 83.500$, $Z = -4.389$, $P < 0.01$) and WBC counts ($U = 145.000$, $Z = -3.186$, $P < 0.01$) in the complex anal fistula group were significantly higher than those in the simple anal fistula group. Meanwhile, the Cliff's delta values for CRP levels and WBC counts were − 0.729 and − 0.529, respectively, both of which were classified as large effect sizes per standard Cohen's effect size interpretation criteria, indicating that the between-group differences were not only statistically significant, but also of extremely strong clinical relevance. Furthermore, pairwise comparisons with Dunn's t correction (Table 10) demonstrated extremely statistically significant differences in the distribution of WBC counts and CRP levels between the two groups.

Table 8
ANOVA of Groups by the Number of Fistula Tracts

Group (n = 50)	**eDII**
Simple Fistula (n = 28)	0.50 ± 1.80
Complex Fistula (n = 22)	2.86 ± 1.70
F	22.385
η^2	0.318
P	$p < 0.01$

Table 9
Mann–Whitney Test based on the Number of Fistula Tracts

	Anal Fistula Complexity M (P_{25}, P_{75})		Mann–Whitney Test Statistic *U*-value	Mann–Whitney Test Statistic *z*-value	Cliff's delta	*p*
	Simple Fistula (*n* = 28)	Complex Fistula (*n* = 22)				
CRP	1.615 (0.9,5.9)	17.700 (11.0,62.1)	83.500	-4.389	-0.729	$p < 0.01$
WBC	6.615 (5.8,7.8)	9.430 (7.0,12.9)	145.000	-3.186	-0.529	$p < 0.01$

Table 10
Pairwise Comparison of Dunn's t-test Results by the Number of Fistula Tracts

CRP	Group (I)	Group (J)	Median (I)	Median (J)	Mean Difference (I-J)	*p*
	Simple Fistula	**Complex Fistula**	**1.615**	**17.700**	**-16.085**	***p* < 0.01**
WBC	Simple Fistula	Complex Fistula	6.615	9.430	-2.815	$P < 0.01$

3.5.3 Grouping by the Location of Fistula Tracts

The results (Table 11) showed significant differences in the eDII between patients with low and high anal fistula ($P < 0.01$). The eDII of patients with high anal fistula was significantly higher than that of those with low anal fistula. The Mann–Whitney *U* test (Table 12) revealed no statistically significant difference in WBC counts between patients in the low and the high anal fistula groups ($P = 0.129$). In contrast, a statistically significant difference in CRP levels was observed between the two groups ($P < 0.05$). Pairwise comparisons with Dunn–Bonferroni correction further confirmed that CRP levels in the high anal fistula group were significantly higher than those in the low anal fistula group. Meanwhile, the Cliff's delta for CRP levels (Table 13) was − 0.349, which was classified as a medium effect size per Cohen's standard effect size interpretation criteria, indicating that the between-group differences were not only statistically significant, but also of definite clinical relevance.

Table 11
ANOVA Results for Groups Classified by Fistula Location

Group	eDII
Low Anal Fistula (*n* = 34)	1.03 ± 2.07
High Anal Fistula (*n* = 16)	2.63 ± 1.78
F	7.045
η^2	0.128
p	0.011

Table 12
Results of Mann–Whitney Test Analysis by Fistula Location

	Fistula Location M (P_{25}, P_{75})		Mann–Whitney Test Statistic *U*-value	Mann–Whitney Test Statistic *z*-value	Cliff's delta	*p*
	Low Anal Fistula (*n* = 34)	High Anal Fistula (*n* = 16)				
CRP	3.050 (1.3,13.2)	11.150 (3.1,69.9)	177.000	-1.976	-0.349	0.048
WBC	6.715 (5.9,9.3)	8.425 (6.8,11.6)	199.000	-1.518	-0.268	0.129

Table 13
Pairwise Comparison of the Results of Dunn's t-test by Fistula Location

CRP	Group (I)	Group (J)	Median (I)	Median (J)	Mean Difference (I-J)	*p*
	Low Anal Fistula	**High Anal Fistula**	**3.050**	**11.150**	**-8.100**	**0.048**
WBC	Low Anal Fistula	High Anal Fistula	6.715	8.425	-1.710	0.129

4. Discussion

This study is the first to use multicenter clinical data to explore and confirm the close cross-sectional correlation between the eDII and the severity and inflammatory response of anal fistula. We found that higher eDII values were independently and positively correlated with elevated levels of systemic inflammatory markers (CRP and WBC) as well as higher anatomical complexity and severity of anal fistula in enrolled patients. To our knowledge, this is the first study to introduce the eDII into the field of anorectal infectious diseases, which fills the gap in the research on the correlation between dietary inflammatory potential and the progression of anal fistula. From the perspective of potential pathophysiological mechanisms, the pro-inflammatory dietary patterns represented by a high eDII, such as high intake of red meat and processed food and low intake of fruits, vegetables and whole grains, have been previously reported to promote immune cells such as macrophages to release inflammatory factors such as IL-6 and TNF-α by activating the nuclear factor

kappa-B (NF-κB) signaling pathway, thereby exacerbating the inflammatory damage to local perianal tissues [17]. Simultaneously, inflammatory factors such as IL-6 and TNF-α can induce high expression of matrix metalloproteinase (MMP)-2 and MMP-9, leading to abnormal degradation of the extracellular matrix and hindering the regeneration and migration of epithelial cells, which may lead to persistent perianal infection, non-healing of the fistula tract, and even the progression from simple fistula to complex fistula [18]. In addition, pro-inflammatory dietary patterns can elevate oxidative stress levels, inhibit the activity of antioxidant enzymes, cause the accumulation of reactive oxygen species (ROS), and worsen the perianal local inflammatory microenvironment [19].

The results of subgroup analyses further confirmed the correlation between the eDII and the severity of anal fistula. Patients with more severe diseases, such as those with high or complex fistulas, showed consistent increments in the eDII and inflammatory indicators. In the Parks Classification, which was independently evaluated by two blinded colorectal surgeons on the basis of preoperative pelvic MRI and intraoperative exploration records, the eDII of patients with supra-sphincteric fistula was significantly higher than that of patients with trans-sphincteric fistula and inter-sphincteric fistula; the eDII of patients with complex fistula was significantly higher than that of patients with simple fistula; and the eDII of patients with high anal fistula was significantly higher than that of patients with low anal fistula, while the levels of inflammatory markers in the above severe disease subgroups all increased synchronously. Specifically, we found that the eDII had the strongest correlation with the CRP level, which is a more sensitive and stable marker of chronic and persistent inflammatory response, suggesting that long-term pro-inflammatory dietary patterns may be more closely related to the persistent local inflammatory state in patients with anal fistula. These results suggested that a high eDII was not only related to the inflammatory status, but also closely related to the complexity and severity of the disease, which may serve as a potential auxiliary evaluation tool for preoperative risk stratification of patients with anal fistula. However, its prognostic predictive value needs to be verified by further prospective follow-up studies.

In summary, the core finding of this hypothesis-generating exploratory cross-sectional study is that a higher eDII is independently and positively correlated with a higher systemic inflammatory burden and more severe anatomical complexity in patients with anal fistula. From the perspective of clinical translation, adjusting dietary structures to reduce the eDII may be a potential auxiliary strategy to improve the systemic inflammatory status of patients with anal fistula. However, future high-quality prospective cohort studies and randomized controlled trials should confirm whether these dietary interventions can promote wound healing, reduce recurrence rate, and optimize clinical prognosis.

Despite these findings, the present study had some limitations. First, this was a multicenter cross-sectional study with a small sample size of 50 patients. It could only clarify the correlation between variables but could not confirm the causal relationship between the eDII and the severity of anal fistula. Second, although the FFQ used in this study has been validated in the Chinese population, it still has inevitable recall bias. Finally, this study did not collect follow-up data on clinical outcomes such as postoperative wound-healing time, anal fistula recurrence rate, and reoperation rate, precluding assessment of the predictive value of eDII for the long-term prognosis of patients. In future studies, we hope to further expand the sample size and carry out a large-scale multicenter prospective cohort study to clarify the causal relationship between pre-onset pro-inflammatory dietary patterns and the progression and prognosis of anal fistula. Simultaneously, we plan to

design a randomized controlled trial of low-eDII dietary interventions for patients with anal fistula to explore the efficacy of dietary interventions in improving inflammatory status and promoting postoperative recovery, and thereby provide high-level evidence-based medical evidence for the clinical application of dietary intervention in the management of anal fistula.

Declarations

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CRediT authorship contribution statement

Hao Wang and Ziwen Wang contributed equally to this work as co-first authors. Hao Wang: Formal Analysis; Writing – original draft. Ziwen Wang: Formal Analysis; Writing – original draft. Zhi Jiang: Data Curation. Zhiyin Deng: Data Curation. Jingkai Wang: Data Curation. Haoyan Li: Data Curation. Lisi Jian: Conceptualization; Supervision; Writing – review & editing. Huacong Zhu: Conceptualization; Supervision; Writing – review & editing.

Declaration of competing interests

The authors declare no competing interests.

Acknowledgments

None.

Ethics Approval Statement

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki (2013 revision). The study protocol was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Ethics Approval No. AE2024-208-01).

Patient Consent Statement

Written informed consent was obtained from all individual participants included in this study prior to enrollment. All participants were fully informed of the study purpose, research procedures, potential risks, and their rights to voluntarily participate and withdraw from the study at any time without adverse consequences.

Consent for publication

Not Applicable

Availability of Data and Materials

The datasets generated and analyzed during the current study contain sensitive clinical information of study participants and are therefore not publicly available to protect their privacy and medical confidentiality. De-identified datasets supporting the conclusions of this article are available from the corresponding authors (Huacong Zhu: 870663914@qq.com; Lisi Jian: 2892185978@qq.com) upon reasonable request and after signing a data use agreement.

Clinical Trial Registration

This study is a multicenter observational cross-sectional study, which does not fall into the category of interventional clinical trials that require mandatory registration under the International Committee of Medical Journal Editors (ICMJE) requirements. Thus, clinical trial registration is not applicable for this study.

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Table 5,6,7

Table 5,6,7 are available in the Supplementary Files section.

Figures

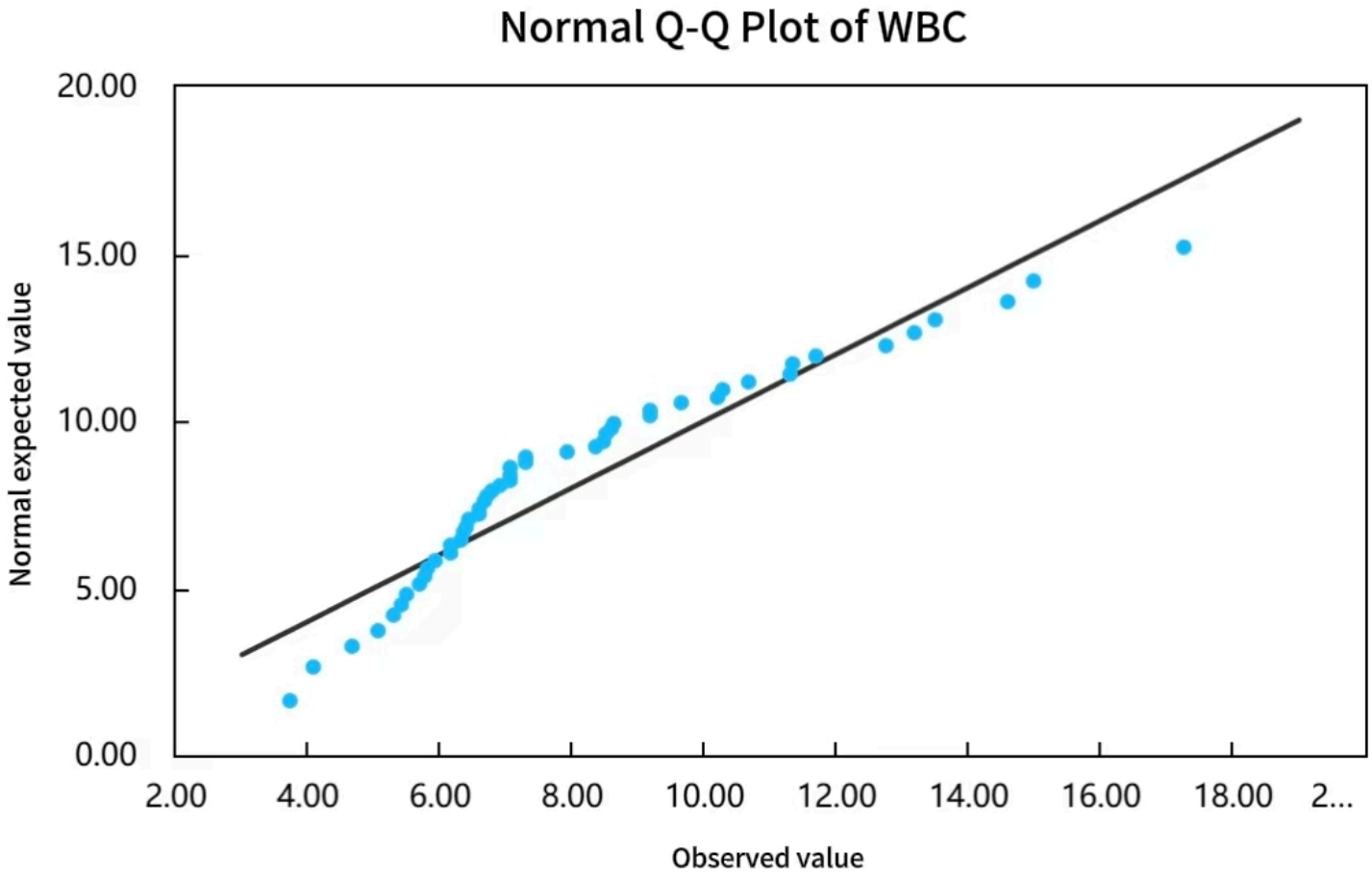


Figure 1

Normal Q-Q Plot of the white blood cell (WBC) count

Note: The Q-Q plot shows that the observed values of the WBC count deviated significantly from the expected normal distribution line, indicating that the WBC count does not follow a normal distribution.

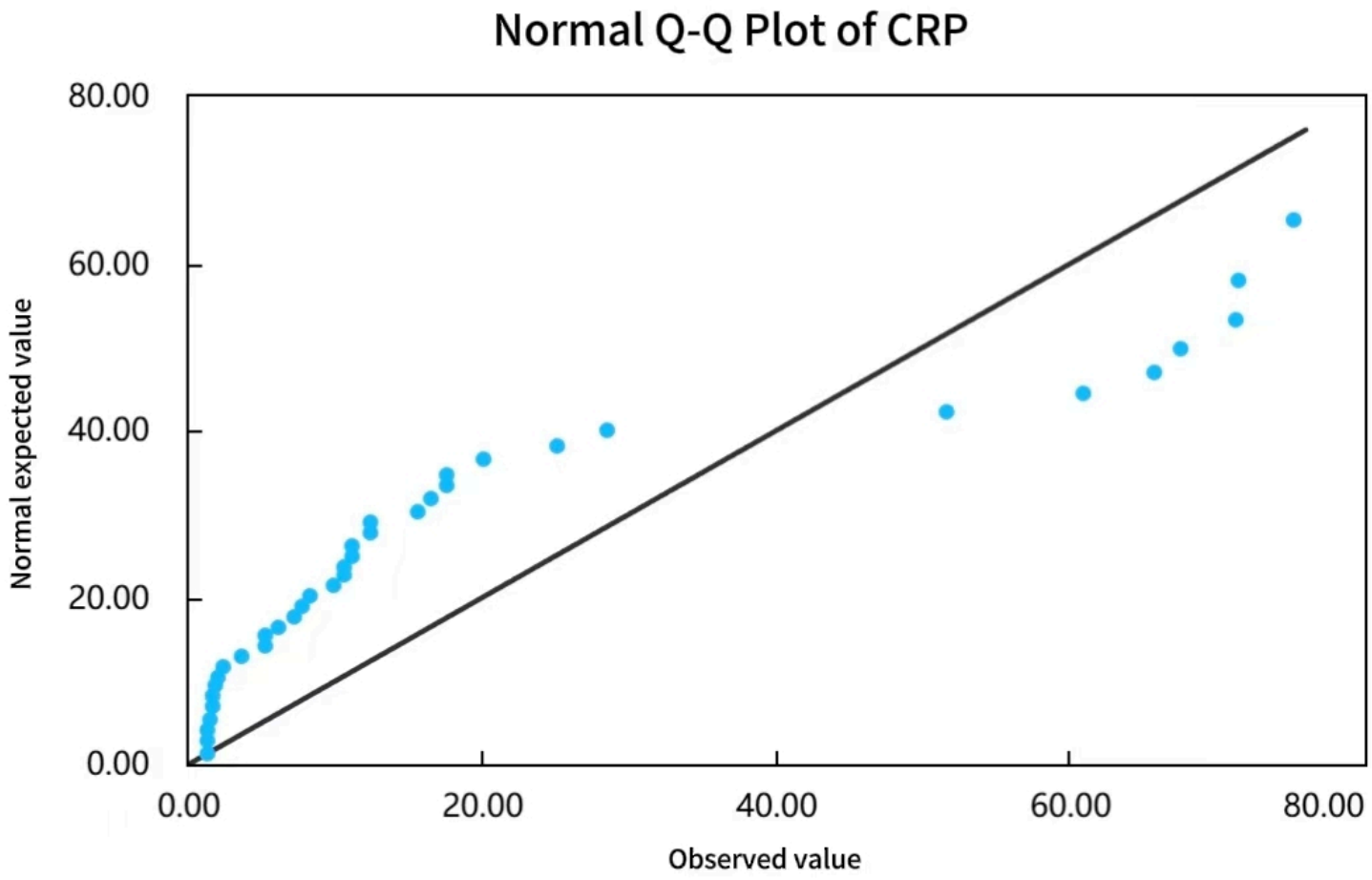


Figure 2

Normal Q-Q Plot of the C-reactive protein (CRP) level

Note: The Q-Q plot shows that the observed values of the CRP level deviated significantly from the expected normal distribution line, indicating that the CRP level does not follow a normal distribution.

Supplementary Files

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- Table567.docx