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ORIGINAL RESEARCH

Blood Lipid Levels and Their Value as Markers of Disease Activity in Severe Ulcerative Colitis

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Purpose: There is limited research on the correlation between blood lipid levels and severe ulcerative colitis, and this article helps to reveal the relationship between the two. This study aimed to explore the relationship between blood lipid levels and disease activity, and to evaluate the early predictive value of blood lipid levels for severe ulcerative colitis (UC).

Patients and Methods: Here, we analyzed blood lipid indicators of 210 patients with UC and 210 healthy individuals who visited the hospital between August 2018 and August 2022. We divided the patients with UC into non-severe and severe groups, analyzed the relationship between blood lipid levels and severe UC, and evaluated the early predictive value of blood lipid indicators for severe UC.

Results: Compared with healthy individuals, patients with UC had lower total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C levels ($P<0.05$). Patients with severe versus non-severe UC had decreased TC, HDL-C, LDL-C, and non-HDL-C levels ($P<0.05$). The combined detection of TC level and erythrocyte sedimentation rate (ESR) predicted a working characteristic receiver operating characteristic curve area of 0.768 (0.694–0.841) in patients with severe UC, which had good early predictive value with a sensitivity of 77.0% and specificity of 66.7%.

Conclusion: TC, HDL-C, LDL-C, and non-HDL-C levels were decreased in patients with severe UC. Combined TC levels and ESRs had good early predictive value for severe UC.

Keywords: erythrocyte sedimentation rate, high-density lipoprotein cholesterol, lipid levels, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, severe ulcerative colitis, total cholesterol, triglyceride, ulcerative colitis

Introduction

Ulcerative colitis (UC) is a chronic nonspecific type of inflammatory bowel disease (IBD) characterized by continuous and diffuse inflammatory changes in the colonic mucosa. Its global prevalence is rapidly increasing.[1,2] Severe flares of UC may be life-threatening,[3] potentially leading to serious adverse consequences such as bleeding, perforation, and toxic megacolon, and may require lifelong treatment. Accurate diagnosis of flares is pivotal for IBD management,[4] however, some patients cannot undergo colonoscopies due to disease severity. Thus, new biomarkers are required to reflect the clinical disease activity of UC.

The examined lipid profile includes total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). Studies have demonstrated that pro-inflammatory cytokines modulate lipolytic enzyme activity, resulting in altered lipid metabolism in UC.[5] HDL-C is known to possess anti-inflammatory effects, and its decrease is associated with inflammatory diseases. During the acute inflammatory stages of UC, dysregulated lipoprotein metabolism results in changes in lipid profiles as reflected by reduced TC and variable TG levels. These changes are more evident during active disease stages. These alternations in lipid profiles closely reflect disease activity and inflammatory status in patients with UC.[6]

Abnormal blood lipids are very common in China, and the main components of abnormal blood lipids differ from those of European and American populations.[7] Differences in blood lipid profiles also exist between UC patients and the

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general population.[5,8] Persistent dyslipidemia is associated with a higher risk of serious disease activity and poorer long-term outcomes in patients with UC.[9]

The relationship between lipid metabolism and critical illness recently received widespread attention.[10] Limited studies have analyzed blood lipid levels in patients with UC, however, the results have been conflicting.[11,12]

This study aimed to analyze the associations between blood lipid profiles (TC, HDL-C, LDL-C, TG, and non-HDL-C) and disease severity in UC patients, and to evaluate their potential as predictive markers for severe UC.

Materials and Methods

Study Participants

This study included 210 patients diagnosed with UC (133 males, 77 females; mean age 52 [37–63] years old) and hospitalized in the Department of Gastroenterology at the First Affiliated Hospital of Shanxi Medical University between August 2018 and August 2022. An additional 210 healthy controls (HC, 127 males, 83 females; mean age, 51 [37–62] years old) were enrolled during the same period as a control group for blood lipid analysis (Figure 1).

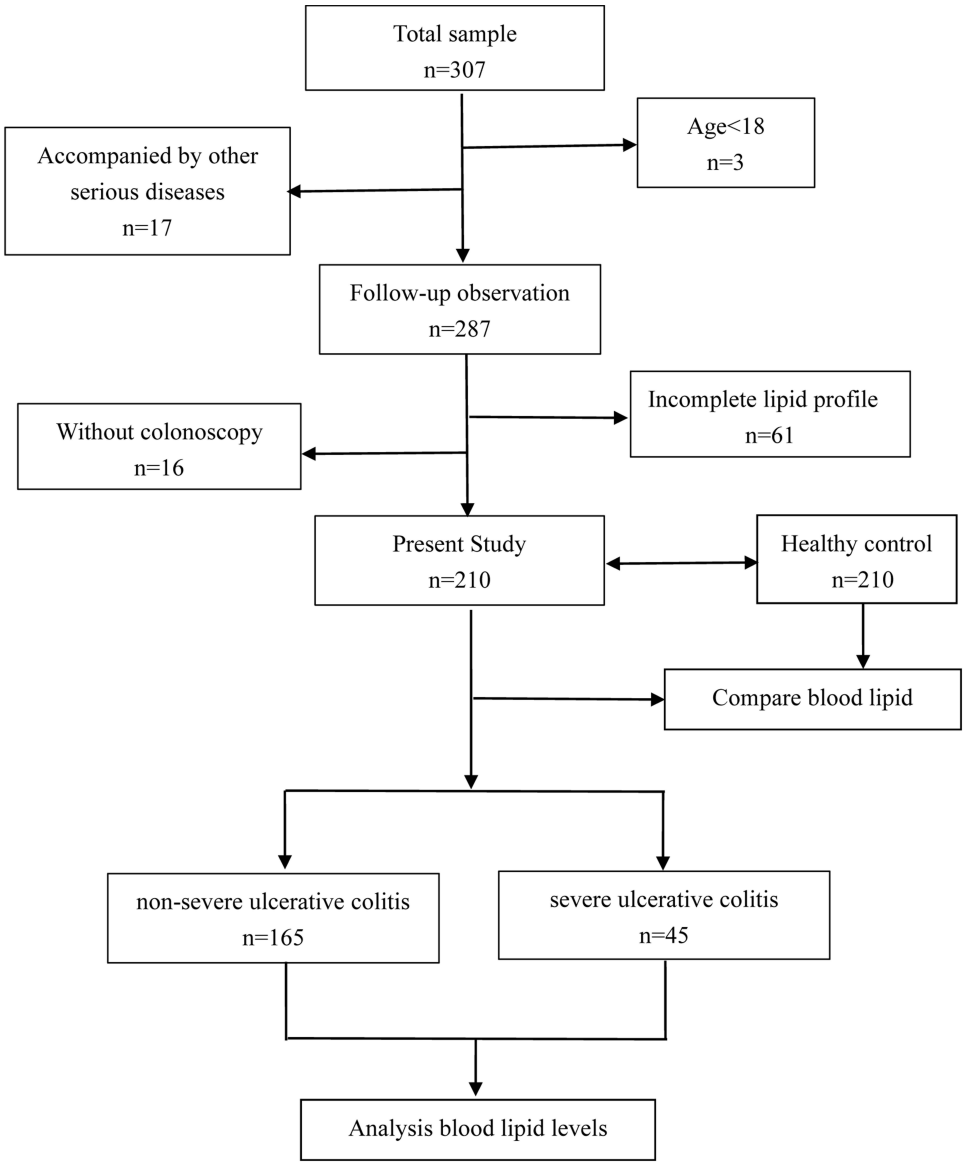

Figure 1 Flowchart of study participants.

Inclusion Criteria

1. Diagnosis of UC based on the European Consensus on the Diagnosis and Treatment of Ulcerative Colitis;[13]
2. Age ≥ 18 years old;
3. Availability of complete clinical data on gender, age, body mass index (BMI), disease course, maximum extent of diagnosis, colonoscopy, and disease activity;
4. Availability of complete blood lipid data, including TC, TG, HDL-C, and LDL-C levels.

Exclusion Criteria

1. Incomplete blood lipid or clinical data;
2. Use of lipid-lowering medication within past 1 month;
3. Complications related to hypertension, diabetes, thyroid dysfunction, and other diseases affecting dyslipidemia;
4. Presence of severe comorbidities (heart failure, liver failure, renal failure, malignant tumors), pregnancy, or lactation.

Blood Lipid Analysis

The enrolled UC patients and HC were fasted for 12 h before blood collection via the antecubital vein.[14] Samples were sent for laboratory analysis of TC, TG, LDL-C, HDL-C, inflammation markers, erythrocyte sedimentation rate (ESR), and hemoglobin levels.

Disease Severity Assessment

The Mayo score (Table 1) was utilized to classify UC disease as mild, moderate, severe, or in remission based on criteria scores.[15] Scores of 0–2 indicate remission, 3–5 mild disease, 6–10 moderate severity, and 11–12 designate severe UC. The Montreal Classification system was also utilized to categorize the extent of UC (Table 2).[16]

Statistics

SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Graphing and data visualization were performed using Sangerbox 3.0 (http://vip.sangerbox.com/login.html) and GraphPad Prism 9.0 software (GraphPad Software, San Diego, CA, USA). Continuous variables are represented as mean ± standard deviation or median (interquartile range). Categorical variables are represented as numbers and proportions. Group differences in qualitative/quantitative variables were evaluated using the Chi-squared test or Fisher's exact test, while independent samples

Table 1 Mayo Scoring System for UC Activity

Mayo Index	0	1	2	3
Stool Frequency	Normal	1–2/day > Normal	3–4/day > Normal	5/day > Normal
Rectal bleeding	None	Streaks of blood with stool less than half of the time	Obvious blood with stool most of the time	Blood alone passed without stool
Findings on endoscopy	Normal	Erythema, decreased vascular pattern, and mild friability	Marked erythema, lack of vascular pattern, friability, and erosions	Spontaneous bleeding and ulcerations
Physician's global assessment	Normal	Mild	Moderate	Severe

Table 2 Montreal Classification of UC

Extent	Disease involvement	Anatomy
E1	Ulcerative proctitis	Isolated rectal involvement
E2	Left-sided disease	Disease involving rectum and sigmoid colon but not beyond the splenic flexure
E3	Extensive colitis	Disease involvement beyond the splenic flexure

t-tests or Mann–Whitney *U*-tests were used to evaluate continuous variables. Asterisk symbols were used to denote statistical significance. Multicollinearity analysis was conducted using the variance inflation factor (VIF) method where variables with a VIF>10 were excluded. Logistic regression analysis was conducted with disease severity as the dependent variable, with steroid taken, disease location, lipid parameters, ESR, and Hb as independent variables, using a forward stepwise selection (α in = 0.05, α out = 0.1). Significant prognostic indicators were selected to construct a receiver operating characteristic (ROC) curve.

Results

Analysis of Blood Lipid Levels in Healthy Controls and UC Patients

To understand the differences in the blood lipid profiles between HC and UC patients, we measured blood samples for TG, TC, HDL-C, LDL-C, and non-HDL-C (Table 3). The results found that compared with the HC group, the UC patient group had significantly lower levels of TC, HDL-C, LDL-C, and non-HDL-C (P<0.001) (Figure 2). No significant differences were observed in TG levels, age, or gender distribution between the two groups. These findings revealed a difference in the blood lipid profile between UC patients and healthy controls.

Comparison of Clinical Characteristics Between Non-Severe and Severe UC Patients

We further classified the UC patients into groups based on the Mayo Scoring system. Subsequently, we collected and compared the clinical data between non-severe and severe UC patients (Table 4). The non-severe UC group included 165 patients (102 males, 63 females; median age, 50.71 [34.75–66.67] years old). The severe UC group included 45 patients (31 males, 14 females; median age, 51.02 [35.79–66.25] years old). Based on the Montreal classification of UC extent, the non-severe UC groups comprised 24.24% proctitis (E1), 29.7% left-sided colitis (E2), and 46.06% extensive colitis (E3). In comparison, the severe UC group comprised 0.00% proctitis (E1), 17.78% left-sided colitis (E2), and 82.22% extensive colitis (E3). The severe group had a significantly wider range of colonic involvement (P<0.001). There was no significant difference between severe and non-severe groups in terms of disease course, initial/recurrent symptoms, smoking status, alcohol consumption, or BMI. However, there was a significant difference in the extent of colon involvement. Additionally, we observed that patients with severe UC demonstrated higher steroid use.

Blood Lipid Levels and Biochemical Indicators of Non-Severe Versus Severe UC Groups

We further evaluated the relationship between blood lipid levels and the patterns of colonic involvement in severe and non-severe UC patients. We found that patients with severe UC had significantly lower levels of TC, HDL-C, LDL-C, and non-HDL-C compared to those with non-severe UC (P<0.05) (Figure 3a–d and Table 5).

The Mayo scoring system, ESR, and hemoglobin levels reflect UC activity. The mean Mayo score was higher in the severe group (12.00 [11.00–12.00]) than in the non-severe group (5.00 [4.00–8.00]) (P<0.001). The average ESR was also higher for severe UC (30.00 [15.00–46.00] mm/h) versus non-severe UC (15.00 [7.00–25.00] mm/h), while the

Table 3 Blood Lipid Levels in Healthy Controls and Patients with UC

Variables	HC Group	UC Group	*P*-value
Gender (male/female)	127/83	133/77	0.547
Age (years old)	51 (37–62)	52 (37–63)	0.748
TC (mmol/L)	4.52 (3.78–5.26)	3.68 (2.70–4.66)	<0.001
TG (mmol/L)	1.15 (0.84–1.52)	1.09 (0.86–1.45)	0.767
HDL-C (mmol/L)	1.32 (1.17–1.49)	0.95 (0.82–1.09)	<0.001
LDL-C (mmol/L)	2.72 (2.05–3.39)	2.37 (1.65–3.09)	<0.001
Non-HDL-C (mmol/L)	3.17 (2.43–3.91)	2.71 (0.87–3.55)	<0.001

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

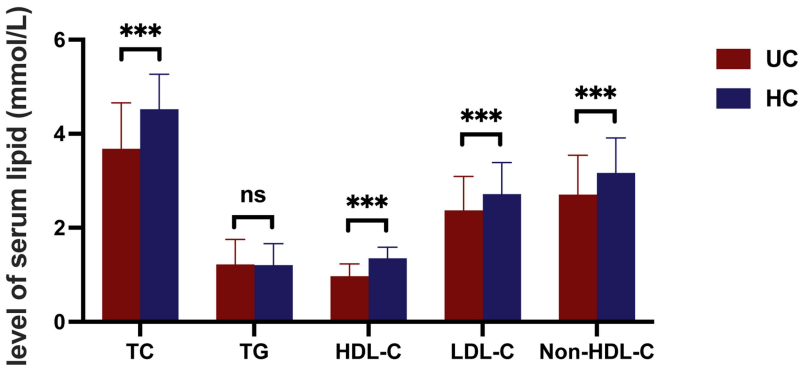

Figure 2 Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C levels were lower among patients with ulcerative colitis than in healthy controls. ***P<0.001.

mean hemoglobin level was significantly lower in the severe group (110.40 [86.61–134.19] g/L) compared to the non-severe group (126.69 [103.92–149.46] g/L) (P<0.001), (Figure 3f–h). No significant difference in TG levels was observed between the two groups (Figure 3e).

Table 4 Basic Clinical Characteristics of Patients with Non-Severe Versus Severe UC

Variables	Non-Severe	Severe	*P*-value
Age (years)	50.71 (34.75, 66.67)	51.02 (35.79, 66.25)	0.906
Gender (%)			0.383
Male	102 (61.82)	31 (68.89)	
Female	63 (38.18)	14 (31.11)	
Disease duration (%)			0.928
<10 years	133 (80.61)	36 (80.00)	
≥10 years	32 (19.39)	9 (20.00)	
Maximum extent diagnosed (%)			<0.001
E1	40 (24.24)	0 (0.00)	
E2	49 (29.70)	8 (17.78)	
E3	76 (46.06)	37 (82.22)	
Initial/Recurrent (%)			0.242
Initial	44 (26.67)	16 (35.56)	
Recurrent	121 (73.33)	29 (64.44)	
Smoking (%)			0.153
Never	126 (76.36)	29 (64.4)	
Former	25 (15.15)	8 (17.8)	
Current	14 (8.49)	8 (17.8)	
Drinking (%)			0.136
Never	136 (82.42)	35 (77.8)	
Former	18 (10.91)	3 (6.7)	
Current	11 (6.67)	7 (15.6)	
BMI (kg/m^2)	21.63 (18.32, 24.94)	20.81 (17.82, 23.80)	0.138
Therapeutic drugs (%)			
5-ASA	145 (87.88)	43 (95.56)	0.175
Steroids	8 (4.85)	23 (51.11)	<0.001
Immunosuppressants	2 (1.21)	2 (4.44)	0.202
Biotherapy	10 (6.06)	3 (6.67)	0.555

Abbreviations: BMI, body mass index; 5-ASA, 5-aminosalicylic acid.

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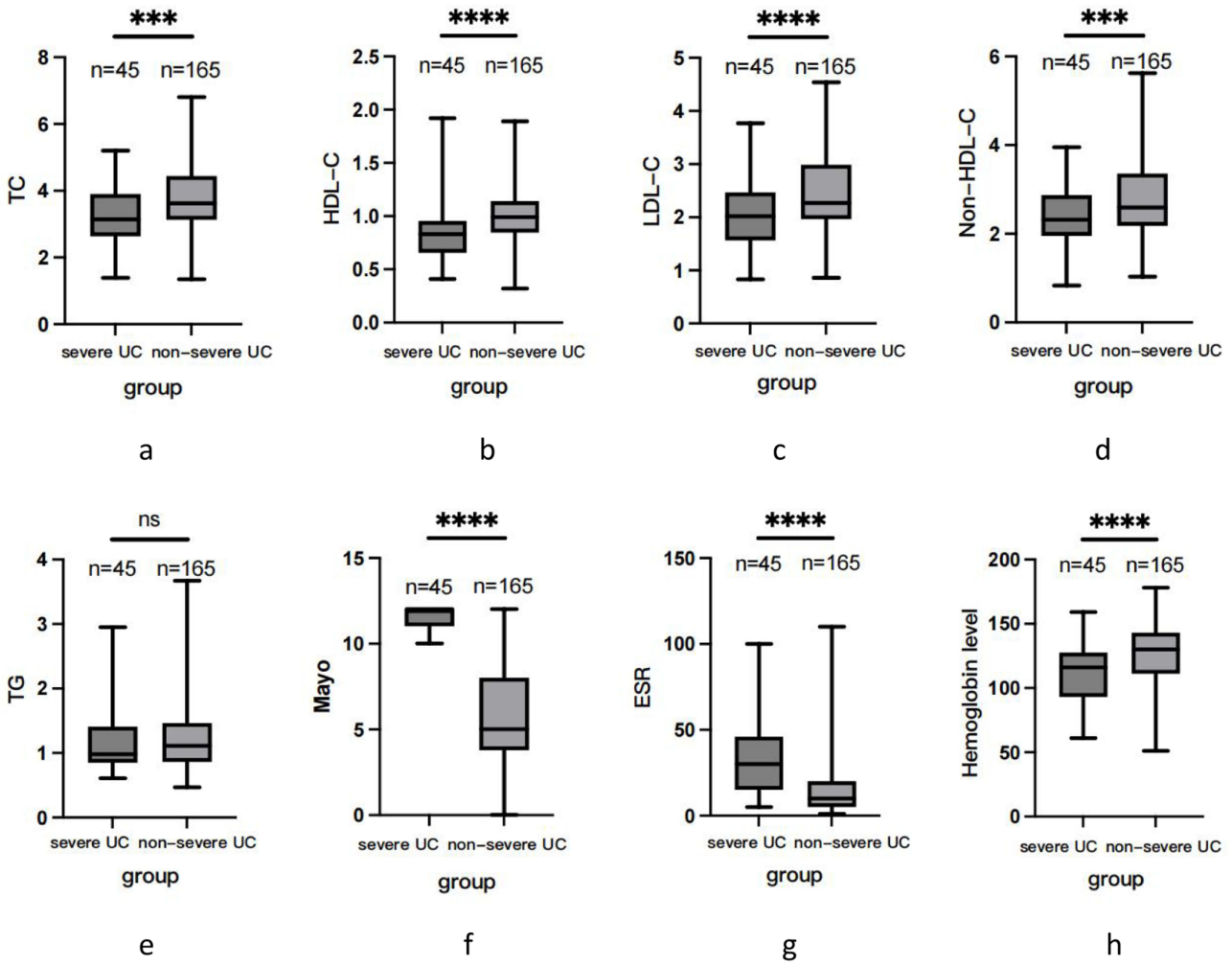

Figure 3 Compared to the non-severe ulcerative colitis (UC) group, the severe UC group had lower levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C (**a**–**d**). There was no statistically significant intergroup difference in TG (**e**). The Mayo score and erythrocyte sedimentation rates (ESRs) were higher in the severe versus non-severe group, while the hemoglobin level was lower in the severe versus non-severe group (**f**–**h**). ****P<0.001, ***P<0.05, ^{ns}P>0.05.

Due to potential multicollinearity among lipid parameters, correlation analyses were conducted. The results showed that TC, LDL-C, and non-HDL-C were strongly correlated (VIF>10) (Supplementary Table 1). After excluding LDL-C and non-HDL-C, the remaining variables had a VIF<5 and were analyzed subsequently. Logistic regression analysis was performed with disease

Table 5 Blood Lipid Levels and Biochemical Indicators of Non-Severe Versus Severe UC Groups

	Non-Severe	Severe UC	*P*-value
Mayo scores	5 (4.0, 8.0)	12 (11, 12)	<0.001
BMI	21.63 (18.32, 24.94)	20.81 (17.82, 23.80)	0.138
TC	3.81 (2.84, 4.78)	3.22 (2.34, 4.1)	<0.011
TG	1.11 (0.86, 1.47	0.98 (0.85, 1.41)	0.714
HDL-C	0.99 (0.85, 1.14)	0.83 (0.66, 0.96)	<0.001
LDL-C	2.46 (1.75, 3.17)	2.04 (1.40, 2.68)	<0.001
Non-HDL	2.80 (2.16, 3.64)	2.37 (1.65, 3.09)	0.002
ESR	15 (7, 25)	30 (15, 46)	<0.001
Hb	126.69 (103.92, 149.46)	110.40 (86.61, 134.19)	<0.001

Abbreviations: BMI, body mass index; TC, Total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ESRs, erythrocyte sedimentation rates; Hb, hemoglobin.

severity as the dependent variable and with steroids taken, E1, E2, E3, TC, HDL-C, ESR, and Hb as independent variables (Supplementary Table 2). The results from forward stepwise regression (forward: lr; α in=0.05, α out=0.10) revealed that TC (OR=1.736, 95% CI: 1.133–2.68) and ESR (OR=0.968, 95% CI: 0.953–0.984) were significantly associated with UC severity (Figure 4).

Predictive Value of TC Level and ESR for Severe UC

To determine the clinical significance of TC levels and ESR in predicting severe UC, ROC curves were constructed and predictive values were calculated. TC level yields an area under the ROC curve (AUC) of 0.665 (95% CI: 0.574–0.756) for predicting severe UC, with a cutoff of 2.955 mmol/L, sensitivity of 83.6%, and specificity of 42.2% (Figure 5a). Meanwhile, the AUC of ESR for predicting severe UC was 0.253 (95% CI: 0.172–0.334), with a cutoff of 105 mm/h, sensitivity of 6%, and specificity of 0% (Figure 5a), indicating a poor predictive capability. Using logistic regression to combine TC level and ESR improved the AUC to 0.768 (95% CI: 0.694–0.841) for predicting severe UC, with a sensitivity of 77.0% and a specificity of 66.7%, which was superior to either marker alone (Figure 5b).

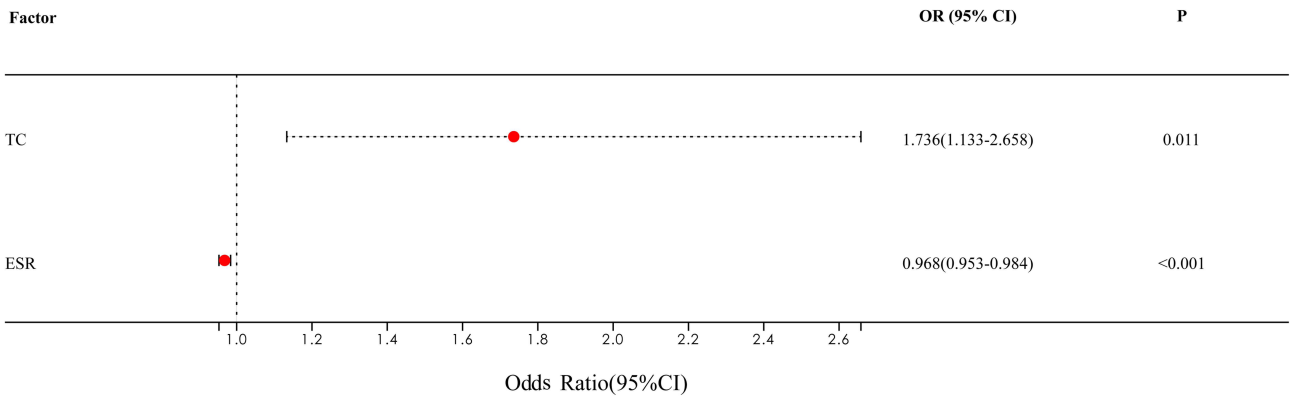

Figure 4 Total cholesterol (TC) level (odds ratio, 1.736) was a risk factor for severe UC, whereas erythrocyte sedimentation rate (ESR) (odds ratio, 0.968) was a protective factor for severe UC.

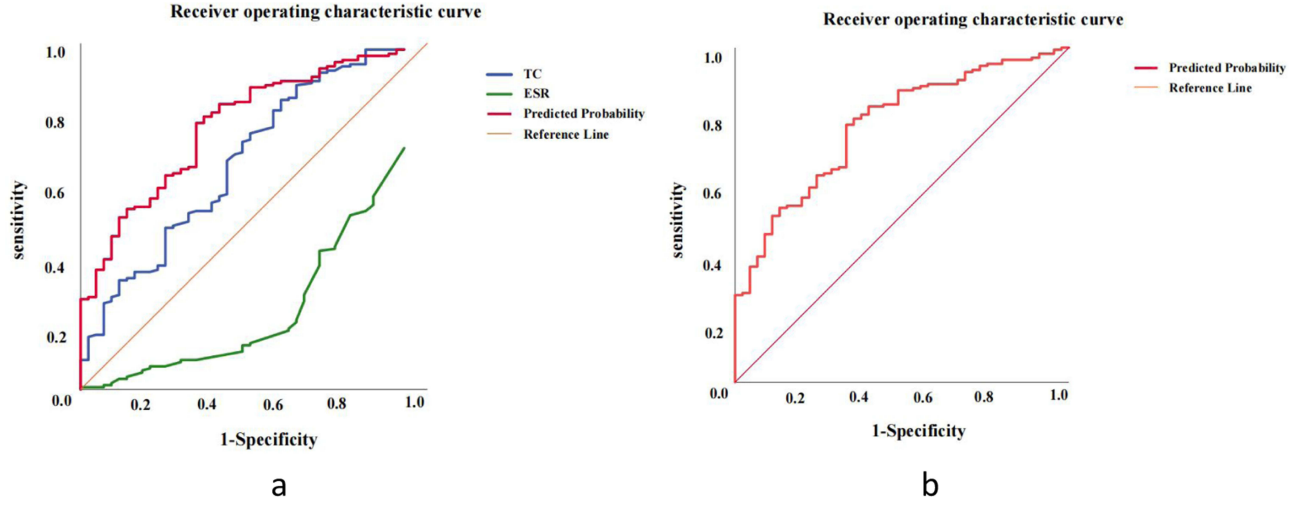

Figure 5 Total cholesterol (TC) predicted an area under the receiver operating characteristic curve (AUC) (95% confidence interval) of 0.665 (0.574–0.756) for severe UC. ESR predicted an AUC (95% confidence interval) of 0.253 (0.172–0.334) for severe UC (**a**). TC and ESR used together predicted an AUC (95% confidence interval) of 0.768 (0.694–0.841) for severe UC (**b**).

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Discussion

Although colonoscopy remains the gold standard for evaluating UC severity, the invasive nature limits its utility and acceptability.[4] Therefore, identifying accurate, noninvasive biomarkers to assess UC activity is imperative for improving patient care and outcomes.

Compromised intestinal barrier integrity in UC often triggers aberrant immune responses, resulting in symptoms like enteritis, malabsorption, and altered lipid metabolism, which may provide insight into disease activity and severity.[5,8,9] The various lipid changes in UC likely stem from complex interplay between inflammatory cytokines, malnutrition, intestinal injury-induced malabsorption, and surgical resection.

Overall serum lipid levels are lower in patients with UC than in healthy individuals and are negatively associated with disease severity.[17] However, studies have shown TG levels do not significantly differ between UC patients and healthy controls.[5] Aligning with these findings, our study demonstrates that the levels of TC, HDL-C, LDL-C, and non-HDL-C were lower in patients with severe UC compared to non-severe patients. TG levels were comparable between these two groups, which may be attributed to the frequent use of steroids, immunosuppressants, and other TG-influencing medications to manage inflammation in active UC.[18] The lack of difference in TG levels could also be related to dietary and metabolic factors,[19,20] as TG levels are impacted by nutrition and metabolism. Thus, similarities in the regional diets of study participants may contribute to the consistent TG levels observed between the UC patients and healthy controls.

Altered TC levels have been associated with other systemic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and chronic heart failure.[21,22] This relates to the inflammatory state and elevated inflammatory markers.[23] Interestingly, while TC emerges as a risk factor for severe UC in our study, patients with severe UC showed lower TC levels. This observation indicates that inflammatory changes may occur before clinical manifestations in UC patients.[24] The observed dyslipidemia associated with UC possibly results from increased catabolism rather than decreased generation.[25] Similarly, decreased TC levels relate to inflammation in UC as well.[26] Inflammation-induced decreases in TC and LDL-C may stem from increased highly inflammatory small dense LDL-C levels.[8] Inflammation inhibits cholesterol synthesis and as inflammation resolves, TC levels can increase. In alignment with our findings, patients with severe UC exhibited significantly lower TC levels than non-severe patients,[27] positioning TC as a potential predictive marker of UC severity.

TC levels are decreased in patients with IBD compared to healthy controls, correlating with disease activity and increasing with treatment.[28,29] The reduction in TC and LDL-C may be due to increased small dense LDL particles, which are more pronounced in severe inflammation.[8,30] Erythrocyte sedimentation rate (ESR), a measure of inflammation, is often elevated with UC disease activity.[31] Although ESR is a commonly used inflammatory marker for assessing UC severity, and very few studies have examined the relationship between cholesterol levels and UC severity. This study found that ESR combined with TC levels can be used to assess the severity of UC. Moreover, we demonstrate that combining ESR and TC biomarkers improves identification of severe UC. These non-invasive indicators, together with colonoscopies, can better monitor UC progression and guide treatment. Further research on non-invasive biomarkers like these can reduce patient suffering and medical costs. After adjusting for steroid use and disease location in a logistic regression analysis, we found that TC level was significantly associated with UC severity and that steroid use and extensive disease location were independent risk factors. Our findings summarize this important research area and provide a framework for future investigation.

Limitations and Shortcomings

This study has several limitations that warrant consideration. First, it was a retrospective single-center investigation performed at a large provincial tertiary hospital treating a high volume of complex UC cases. This specialized patient population could have introduced a selection bias. Second, blood lipid testing was ordered at the discretion of individual health providers during diagnosis and treatment courses. Younger UC patients in particular may not have had routine lipid profiling completed. Additionally, due to incomplete patient follow-up data, we were unable to determine the association between lipid profiles and important clinical outcomes, such as 30-day hospitalization and colectomy rates. Furthermore, although logistic regression adjusting for steroid use and disease location was conducted, adjusted versus unadjusted comparisons were not performed. In the future, we will include more thorough multivariate analyses to adjust

for additional confounders such as smoking status, alcohol consumption, and BMI, to learn how these factors affect the relationship between blood lipid levels and UC disease severity. Large-scale multicenter studies are still needed to delineate the relationship between blood lipids and UC severity more definitively, as well as validate the prognostic utility of circulating lipid levels in predicting severe UC flares. Accounting for the heterogeneity in lipid testing patterns among different provider practices and age groups would strengthen future findings.

Conclusion

Our study shows that UC patients exhibit significantly decreased TC, HDL-C, LDL-C, and non-HDL-C levels. After adjusting for confounders, TC levels demonstrate a significant association with the severity of UC. Moreover, the combination of TC and ESR revealed promising predictive value for identifying severe UC. These findings indicate a potential utility of the blood lipid profile in personalized treatment and prognostic prediction in clinical management of severe UC.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Research Ethics Review Committee of the First Hospital of Shanxi Medical University (KYLL-2023-246). Informed consent was waived due to the retrospective nature of this study. All study personnel signed confidentiality agreements and committed to safeguarding patient information, which was used solely for the purposes of this research.

Data Sharing Statement

The data utilized in this study are available from the corresponding author upon reasonable request.

Acknowledgment

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Author Contributions

All authors made significant contributions to the conception, study design, data collection, analysis, and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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