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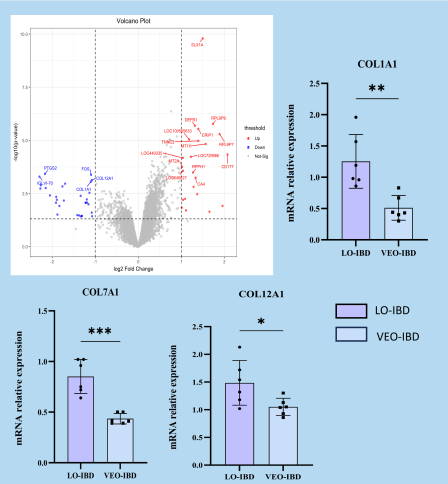
Collagen Expression Downregulation and Intestinal Barrier Impairment are Associated with Severe Clinical Phenotypes in Very Early-Onset Inflammatory Bowel Disease

Study design

- single-center retrospective cohort study
- Objective: To compare VEO-IBD and LO-IBD across clinical, endoscopic, and transcriptomic profiles.
- Methods: We retrospectively analyzed clinical data from 76 children (2010-2025) and leveraged the transcriptomic dataset GSE57945 (20 VEO-IBD vs. 260 LO-IBD).

Key result



Conclusion

- VEO-IBD exhibits more severe clinical phenotypes, which may be associated with collagen-mediated intestinal barrier dysfunction.

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Collagen expression downregulation and intestinal barrier impairment are associated with severe clinical phenotypes in very early-onset inflammatory bowel disease

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Ethical Appproval

This study was approved by the Ethics Committee of Tangdu Hospital, Fourth Military Medical University (Approval Number: K202501-05) and conducted in accordance with the Declaration of Helsinki principles. This retrospective study received a waiver of informed consent. All data were collected anonymously to protect the privacy of participating children.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Author contributions

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All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafting and revising the manuscript and have approved the final version of the manuscript.

Data Availability

The clinical patient data used in this study involve patient privacy and ethical considerations; their use requires author authorization. Requests for access should be submitted to the corresponding author. The intestinal tissue transcriptome data were derived from the public GEO database, dataset GSE57945, and can be directly accessed and downloaded through the NCBI GEO platform.

Acknowledgements

The authors would like to thank all the patients and their families who have participated in this study.

Abstract

Background: The global incidence of pediatric inflammatory bowel disease (IBD) is increasing steadily. Children with IBD under 6 years present unique clinical characteristics.

Objective: To compare very early-onset IBD (VEO-IBD) and late-onset IBD (LO-IBD) across clinical, endoscopic, and transcriptomic profiles.

Methods: We retrospectively analyzed clinical data from 76 children (2010-2025) and leveraged the transcriptomic dataset GSE57945 (20 VEO-IBD vs. 260 LO-IBD).

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Result: VEO-IBD patients showed significantly higher rates of hematochezia (*RR*=1.552, *95% CI*:1.099~2.191, *P*=0.032), fever (*RR*=1.696, *95% CI*:1.093~2.631, *P*=0.034), decreased serum creatinine (*RR*=1.588, *95% CI*:1.251~2.016, *P*=0.004), and higher Mayo scores (*t*=2.232, *95% CI*:1.852~3.407, *P*=0.030). Transcriptomics revealed significant downregulation of collagen genes (COL12A1, COL1A1, COL7A1) in VEO-IBD, confirmed by qRT-PCR.

Conclusion: VEO-IBD exhibits a more aggressive phenotype than LO-IBD, which may be associated with distinct clinical severity and collagen-related barrier dysfunction. These findings suggest a novel pathophysiological hypothesis linking extracellular matrix impairment to disease severity in VEO-IBD.

Keywords: VEO-IBD. Clinical phenotype. Transcriptomics.

1.Introduction

IBD is a group of chronic, relapsing disorders of the gastrointestinal tract whose pathogenesis involves a complex interaction of genetic susceptibility, environmental factors, and immune dysregulation [1].Epidemiological data indicate that the global incidence of IBD continues to rise[2]. Approximately 25% of patients develop the condition before the age of 18,and cases occurring before age 6 are defined as VEO-IBD[3]. VEO-IBD is associated with genetic defects[4], clinically characterized by higher disease activity and more severe growth retardation[5,6]. Over 80 causative genes have been implicated, often disrupting epithelial barrier function and immune regulation[7]. However, research has predominantly focused on immune dysfunction, while the role of epithelial barrier integrity, particularly collagen-mediated structural support, remains less explored. Collagens (e.g., COL1A1, COL7A1) are crucial for mucosal integrity. Their dysregulation could impair barrier function, potentially facilitating bacterial translocation and exacerbating inflammation. This mechanism may be one factor contributing to the aggressive phenotype observed in VEO-IBD. This study aimed to systematically compare the clinical and molecular features of VEO-IBD and LO-IBD. We integrated retrospective

clinical data with public transcriptomic analysis to identify key differences and explore the role of collagen expression in disease pathogenesis.

2. Materials and Methods

2.1 Study Design and Participants

This single-center retrospective cohort study included children (<17 years) diagnosed with IBD at Tangdu Hospital, Fourth Military Medical University between 2010 and 2025. Diagnosis followed ESPGHAN Porto Criteria[8]. Patients were stratified into VEO-IBD (age ≤6 years, n=19) and LO-IBD (age >6 years, n=57) groups. Clinical data were collected from hospital records.

2.2 Clinical Data Analysis

Data were analyzed using SPSS 23.0 (IBM SPSS Statistics, Version 23.0; IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were presented as mean ± standard deviation and compared with the independent samples t-test, while non-normally distributed ones were shown as median (interquartile range) and compared with the Mann-Whitney U test. Categorical variables were presented as number (n) and percentage (%) and compared using the Chi-square or Fisher's exact test, with risk ratios (RR) and 95% confidence intervals (CI) reported where applicable. Recognizing that statistical testing was performed across multiple clinical indicators, P-values should be interpreted with awareness of the potential for increased Type I error. A two-sided P-value < 0.05 was considered statistically significant.

2.3 Transcriptomic Analysis

RNA-seq data from the GEO dataset GSE57945 (20 VEO-IBD, 260 LO-IBD) were analyzed. Differentially expressed genes (DEGs) were identified using the edgeR package (|log2FC| ≥ 1, adjusted P<0.05). Functional enrichment [Gene Ontology

(GO), Kyoto Encyclopedia of Genes and Genomes (KEGG)]and protein-protein interaction (PPI) network analyses were performed. Key collagen gene expression (COL12A1, COL1A1, COL7A1) was validated by qRT-PCR in clinical samples. Statistical significance was defined as * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

3. Results

3.1 Comparison of Clinical Characteristics

3.1.1 Clinical Characteristics

Among 76 pediatric IBD patients (78.9% UC, 17.1% CD), 25% were VEO-IBD. The median age at diagnosis of IBD was 10.75 (IQR: 6.25, 12) years, with 50 males (65.8%) and 26 females (34.2%). The mean age and weight in the VEO-IBD group were 4.00 ± 1.62 years and 16.91 ± 5.40 kg. In contrast, the LO-IBD group had a median age of 11 years (IQR: 9.5–13) and a median weight of 35.7 kg (IQR: 29–49.5). The most common symptoms were abdominal pain (69.7%), diarrhea (59.2%), hematochezia (57.9%), and fever (47.4%). Hematochezia (*RR*=1.552, *95% CI*:1.099~2.191, *P*=0.032) and fever (*RR*=1.696, *95% CI*:1.093~2.631, *P*=0.034) were significantly more frequent in VEO-IBD (Table 1).

3.1.2 Laboratory Indicators and Endoscopic Manifestations in Pediatric IBD

Laboratory findings in pediatric patients with IBD revealed significant inflammatory activation and metabolic disturbances. Specifically, elevated neutrophil percentages and platelet distribution width were observed in more than two-thirds of the patients (77.6% for both parameters). Abnormal coagulation parameters were observed in more than half of the pediatric IBD patients, including elevated platelet counts (56.6%), prolonged prothrombin times (48.7%), and increased fibrinogen levels (43.4%). In addition, 61.8% of the pediatric patients had low hemoglobin levels, but there was no statistically significant difference between the groups. 68.4% of the pediatric patients had decreased creatinine levels, and the

risk of decreased creatinine levels was significantly higher in the VEO-IBD group than in the LO-IBD group (*RR*=1.588*, 95% CI:*1.251~2.016*, P*=0.004). Endoscopic findings showed that the main endoscopic manifestations in pediatric IBD patients were ulcers (82.9%), vascular pattern disruption (53.9%), and fibrinous exudation (28.9%). In addition, inflammatory polyps were observed in six patients (Table 1).

3.1.3 UC Lesion Classification and Mayo Scores in Pediatric Patients

Among 60 pediatric ulcerative colitis cases, the distribution of disease types was as follows: E1 (ulcerative proctitis), 18.3%, E2 (left-sided colitis), 36.7%, E3 (extensive colitis) ,23.3%, and E4 (pancolitis) ,23.3%. The proportion of the E2 subtype was significantly higher in the VEO-IBD group than in the LO-IBD group (P = 0.025). Additionally, the Mayo endoscopic score was significantly higher in the VEO-IBD group compared to the LO-IBD group (*t*=2.232*, 95% CI:*1.852~3.407*, P*=0.030) (Table 2).

3.2 Transcriptomic analysis results

This study utilized the GSE57945 dataset from the GEO database to compare intestinal transcriptomic profiles between children with VEO-IBD and those with LO-IBD (aged 7–17 years). A total of 54 DEGs were identified based on the screening criteria of $|\log_2 FC| \geq 1$ and $P < 0.05$. Key downregulated genes included collagen genes COL12A1, COL1A1, and COL7A1 (Figure 1A). qRT-PCR confirmed significant downregulation of COL12A1, COL1A1, and COL7A1 in VEO-IBD intestinal samples (Figure 1F). GO analysis revealed that DEGs were primarily enriched in processes such as granulocyte migration, regulation of inflammatory response, and collagen trimer formation (Figure 1B). KEGG analysis indicated significant activation of pathways including cytokine-receptor interactions, Toll-like receptors, and IL-17. (Figure 1C). Analysis of PPI networks revealed close interactions among proteins encoded by collagen genes such as COL12A1, COL1A1, and COL7A1, forming a functionally related module. This suggested they may collaboratively participate in

regulating extracellular matrix structure and barrier integrity. This network also incorporated centrally positioned inflammation-related genes such as IL1B, CXCL8, CCL3, and CCL4, which collectively regulate immune cell chemotaxis and inflammatory responses. (Figures 1D and 1E).

4. Discussion

This study demonstrates that pediatric patients with VEO-IBD exhibit more severe clinical and endoscopic phenotypes compared to those with LO-IBD. Analysis based on external transcriptome data further indicates significant downregulation of key collagen genes (COL12A1, COL1A1, and COL7A1) in intestinal tissues of VEO-IBD children. PPI analysis suggests these collagens may exert synergistic effects in maintaining intestinal barrier function. As pivotal molecules sustaining extracellular matrix integrity, their downregulation may correlate with alterations in the intestinal epithelial barrier.

Among the core symptoms of pediatric IBD, our data revealed that VEO-IBD patients had significantly higher rates of hematochezia and fever, along with higher Mayo endoscopic scores, consistent with previous reports[9]. Our laboratory findings align with the established profile of pediatric IBD, which frequently includes thrombocytosis, hypoalbuminemia, and elevated inflammatory markers[10]. In our cohort, inflammatory indicators were significantly elevated, and over 50% of patients exhibited coagulopathy. Previous studies indicate that systemic inflammation in IBD activates the coagulation cascade while suppressing anticoagulant pathways, increasing thrombosis risk[11]. Thus, coagulation parameters should be dynamically monitored to assess disease activity and thrombotic risk, particularly in children with endoscopically confirmed severe inflammation. Notably, decreased creatinine levels were observed in 72.3% of our pediatric IBD patients, with a significantly higher prevalence in the VEO-IBD. This aligns with previous reports of significantly lower serum creatinine levels in IBD patients compared to healthy individuals[12].

Creatinine levels are closely correlated with muscle mass and age. This finding may partly reflect the physiologically lower creatinine levels observed in younger pediatric patients. Nonetheless, it still suggests that VEO-IBD patients may exhibit more pronounced alterations in metabolic or nutritional status, warranting further investigation.

COL12A1, COL1A1, and COL7A1 are core collagen family members and essential components of the extracellular matrix, playing a crucial role in maintaining the structural integrity of the intestinal barrier. PPI network analysis suggested strong interactions between these three proteins. Previous studies have shown that COL7A1 is the pathogenic mutation gene in children with VEO-IBD[13]. The synergistic downregulation of these collagen genes may collectively contribute to weakened collagen network support, reduced structural stability of the intestinal barrier, and impaired mucosal repair capacity. This study also found that CD177 was significantly upregulated in VEO-IBD intestinal tissue.CD177 plays a key role in immune regulation, and its expression is significantly elevated at both the mRNA and protein levels in IBD patients, correlating positively with inflammatory severity [14] . Excessive recruitment of CD177+ neutrophils can lead to overactivation of the immune response, further exacerbating tissue inflammatory damage. These cells infiltrate in large numbers and cross the intestinal mucosal barrier, disrupting connective proteins such as β-catenin and E-cadherin, thereby impairing epithelial integrity[15].

In summary, this study proposes the hypothesis that collagen-mediated epithelial barrier dysfunction may correlate with the severe clinical phenotype of VEO-IBD, offering a novel perspective distinct from simple immune activation to elucidate the pathogenesis of VEO-IBD. However, this study has several limitations: the single-center retrospective design and small sample size in the VEO-IBD group reduced statistical power, potentially obscuring true associations between variables and limiting the generalizability of conclusions due to single-center selection bias. The 15-year data collection period may have been affected by evolving clinical diagnostic criteria, potentially compromising result stability. The study primarily employed univariate analysis without multivariate adjustment for key confounders such as age

and nutritional status, limiting inferences about independent associations. Transcriptomic data were sourced from public databases, and validation was restricted to the mRNA level, lacking verification at the protein functional level, which makes it difficult to fully support conclusions at the mechanistic level. Given these limitations, the study's conclusions should be interpreted with caution. Furthermore, as findings are based on a single-center cohort, their generalizability requires validation in diverse populations and larger independent cohorts. Future research may focus on the following directions: Conduct gain-of-function or loss-of-function experiments using animal models to establish a causal link between collagen-mediated epithelial barrier dysfunction and severe VEO-IBD phenotypes. Further explore the therapeutic potential of targeting extracellular matrix repair in VEO-IBD treatment, offering novel approaches for clinical intervention in this disease.

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Table 1. Comprehensive Characteristics of Pediatric Inflammatory Bowel Disease Patients: Baseline, Clinical, Endoscopic, Laboratory, and Therapeutic Profiles

Parameters	VEO-IBD(n=19)	LO-IBD(n=57)	*P*-Value
Baseline Characteristics			
Age	4.00±1.62	11(9.5,13)	0.000
Weight	16.91±5.40	35.7(29,49.5)	0.000
UC	17(89.5)	43(75.4)	0.330
CD	1(5.3)	12(21.1)	0.165

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IBDU	1(5.3)	2(3.5)	1
Male	11(57.9)	39(68.4)	0.402
Female	8(42.1)	18(31.6)	
Clinical Manifestations			
Abdominal pain	12(63.2)	41(39.8)	0.471
Diarrhea	11(57.9)	34(59.6)	0.893
Hematochezia	15(78.9)	29(50.9)	0.032
Fever	13(68.4)	23(40.4)	0.034
Constipation	2(10.5)	11(19.3)	0.498
Vomiting	2(10.5)	6(10.5)	1.000
Weight loss	1(5.3)	3(5.3)	0.951
Tenesmus	1(5.6)	2(4.2)	1.000
Extraintestinal Manifestations			
Oral ulcers	0	9(15.8)	0.102
Perianal manifestations	1(5.3)	7(12.3)	0.671
Joint manifestations	1(5.3)	3(5.3)	1.000
Complications			
Thrombosis	0	2(3.5)	1.000
Anemia	3(15.8)	20(35.1)	0.113
Conjunctivitis	0	1(1.8)	0.273
Appendicitis	3(15.8)	9(15.8)	1.000
Superficial gastritis	3(15.8)	22(38.6)	0.067
Malnutrition	1(5.3)	12(21.1)	0.165
Growth retardation	1(5.3)	3(5.3)	1.000
Laboratory			
Elevated neutrophil percentage	13(68.4)	46(80.7)	0.342
Thrombocytosis	12(63.2)	31(54.4)	0.504
Decreased hemoglobin	13(68.4)	34(59.6)	0.495
Reduced hematocrit	13(72.2)	30(63.8)	0.522
Hypoalbuminemia	4(21.1)	10(17.5)	0.740

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Reduced creatinine	18(94.7)	34(59.6)	0.004
Prolonged prothrombin time (PT)	4(21.1)	33(57.9)	0.005
Prolonged activated partial thromboplastin time (APTT)	4(21.1)	28(49.1)	0.032
Elevated fibrinogen	7(36.8)	26(45.6)	0.504
D-dimer	8(42.1)	25(32.9)	0.324
Endoscopic mucosal manifestations			
Congestion	19(100)	57(100)	-
Loss of vascular pattern	9(47.4)	32(56.1)	0.506
Fibrinous exudate	7(36.8)	15(26.3)	0.381
Ulceration	13(68.4)	50(87.7)	0.077
Erosion	11(57.9)	16(28.1)	0.019
Inflammatory polyp	1(5.3)	5(8.8)	1.000

Table 2. Classification of Endoscopic Lesions and Mayo Endoscopic Score in children with UC

Parameters	VEO-IBD(n=17)	LO-IBD (n=43)	P-Value
E1	2(11.8)	9(20.9)	0.712
E2	10(58.8)	12(27.9)	0.025
E3	4(23.5)	10(23.3)	1.000
E4	2(11.8)	14(23.3)	0.310
Mayo endoscopic score	8.47(7.08±9.86)	6.67(5.80±7.55)	0.030

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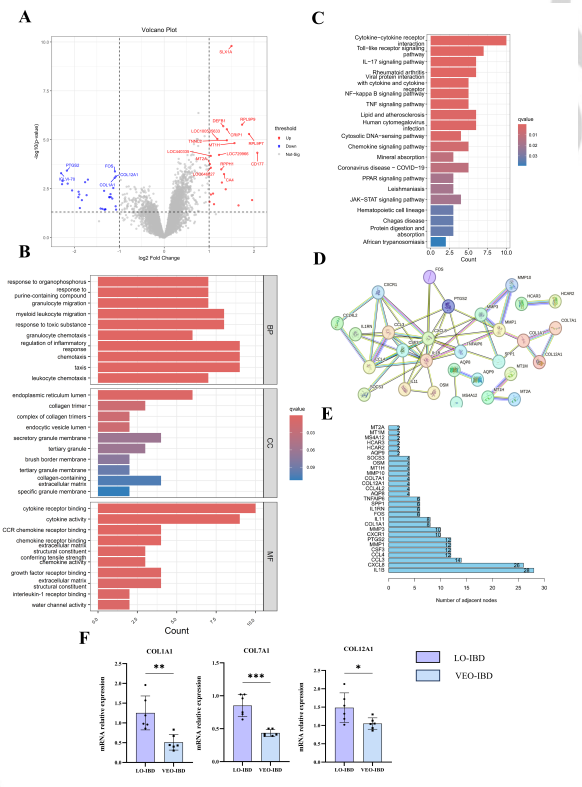

Figure 1. Transcriptomic analysis of intestinal tissue from children with VEO-IBD and

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LO-IBD. A. Volcano plot displaying DEGs between VEO-IBD and LO-IBD groups. B. GO enrichment analysis highlighting significantly enriched terms across biological process, cellular component, and molecular function categories. C. KEGG pathway enrichment analysis showing significantly enriched signaling pathways. D. PPI network showing interactions among proteins encoded by the DEGs. E. Distribution of protein node interactions in the PPI network. F. Validation of COL12A1, COL1A1 and COL7A1 downregulation in Clinical Samples.