ORIGINAL ARTICLE

CONTENTS

The appendix as a full-thickness morphological surrogate for the histological subtype of the colon in patients with chronic slow-transit constipation

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ABSTRACT

Aim: To asses the concordance of histological alterations between appendix and colon in patients with chronic slow-transit constipation (STC) and to determine the feasibility of using the appendix as a full-thickness morphological surrogate for personalizing the extent of colectomy.

Materials and Methods: A single-center retrospective pathomorphological study included 89 patients with CSTC refractory to conservative therapy after colectomy with appendectomy. Full-thickness histological examination of the colon and appendix was performed using semiquantitative assessment of the mucosal, submucosal, muscular, neuronal, and interstitial cells of Cajal (ICC) blocks. Immunohistochemical analysis of ICCs was performed using CD117 (c-kit). Histological profiles were categorized into myopathic, Cajal, neuropathic, and histologically intact subtypes. The concordance of histological phenotypes between the appendix and the colon, the correlation of integrated block scores, and the diagnostic efficacy of the appendix were analyzed.

Results: Within the distribution of colonic phenotypes, the myopathic variant predominated (51.7%), followed by the Cajal subtype (21.3%), the neuropathic subtype (19.1%), and the histologically intact variant (7.9%). The exact match of the histological subtype between the colon and the appendix was achieved in 98.9% of cases, while the concordance of the dominant phenotype reached 100%. Cohen's kappa for exact subtype agreement was 0.985, and the weighted kappa was 1.00. The strongest correlations were identified within the ICC block ($r = 1.00$), the neuronal block ($r = 0.96$), and the muscular block ($r = 0.93$) ($p < 0.001$). For the Cajal subtype, the diagnostic sensitivity, specificity, and overall accuracy of the appendix were 100%.

Conclusions: The appendix demonstrates an exceptionally high concordance with the colonic histological phenotype and can be regarded as a phenotype-predicting, full-thickness morphological surrogate in patients with chronic slow-transit constipation.

KEYWORDS: chronic slow-transit constipation; colectomy; appendix; interstitial cells of Cajal; morphological phenotype.

Wiad Lek. 2026;79(9):2216-2228. doi: 10.36740/WLek/237512 DOI

INTRODUCTION

Chronic constipation is a common functional gastrointestinal disorder and significantly affects patients' quality of life and represents a significant healthcare and social challenge. [1-3]. Chronic slow-transit constipation (CSTC) is a distinct subtype of chronic constipation characterized by delayed colonic transit and often remains refractory to conservative treatment. [4-8]. In such cases, surgical treatment, particularly colectomy, remains one of the most effective options for long-term symptom relief [9]. Despite a decades of colectomy experience for refractory CSTC, the optimal extent of colectomy remains controversial. Various surgical approaches are currently used in clinical practice, ranging from segmental resections to subtotal or total colectomy with ileorectal anastomosis; however, no unified morphological criteria are currently available to guide personalized selection of colectomy extent. [10]. Reported colectomy outcomes demonstrate considerable variability in clinical efficacy, which is likely due to the heterogeneity of the pathogenetic and morphological mechanisms of CSTC [8,11,12]. Contemporary studies indicate that CSTC is not a morphologically homogeneous condition. Structural alterations involving the smooth muscle layer of the colon, the enteric nervous system, the myenteric plexuses, and the interstitial cells of Cajal — which play a pivotal role in the generation and coordination of intestinal motility — have been described in different patients [5, 7, 13]. A reduction in the number or functional impairment of interstitial cells of Cajal, as well as neuropathic and myopathic alterations, may give rise to distinct morphological phenotypes of the disease, which may potentially have different implications for determining the optimal extent of colonic resection [11, 14, 13]. Therefore, the morphological heterogeneity of CSTC may represent one of the factors

contributing to the variability of surgical treatment outcomes. At the same time, the lack of an accessible preoperative method for full-thickness morphological assessment of the colon is a major unresolved problem. Standard endoscopic biopsy is limited to the mucosal layer and does not permit adequate evaluation of the muscular layer, myenteric plexuses, or other transmural alterations that may be critical for morphological phenotyping of CSTC [1, 11, 14]. Consequently, decisions regarding the extent of colectomy are generally made without detailed preoperative understanding of the distribution and severity of neuromuscular pathology. One potential strategy to overcome this limitation is the identification of surrogate morphological marker to predict the dominant colonic histological phenotype preoperatively. The appendix, as a full-thickness structure anatomically and embryologically related to the colon, may represent a potential candidate for such assessment [15]. Laparoscopic appendectomy is a minimally invasive procedure that provides access to full-thickness tissue specimens for comprehensive histopathological evaluation. If histological alterations in the appendix correlate with morphological changes in the colon, this could provide a novel basis for a staged, morphologically guided personalization of surgical strategy. The histological concordance between the appendix and colon in patients with CSTC has not yet been systematically evaluated. Thus, studying this relationship may not only clarify the morphological architecture of CSTC but also offer a new approach to determ the optimal extent of colectomy preoperatively.

AIM

The aim was to asses the concordance of histological alterations between appendix and colon in patients with chronic slow-transit constipation (STC) and to determine the feasibility of using the appendix as a full-thickness morphological surrogate for personalizing the extent of colectomy.

MATERIALS AND METHODS

STUDY DESIGN AND COHORT CHARACTERISTICS

The concordance between the histological phenotypes of the appendix and colon in patients with chronic slow-transit constipation (CSTC) refractory to conservative treatment was studied in a single-center retrospective pathomorphological study. The study included 89 patients who underwent colectomy for CSTC along with appendix.

INCLUSION CRITERIA

Clinically and instrumentally confirmed chronic slow-transit constipation;
Resistance to conservative therapy;
Availability of full-thickness histological specimens of both the colon and appendix;
Absence of previous appendectomy.

EXCLUSION CRITERIA

Hirschsprung disease;
Proctogenic constipation (rectal or pelvic floor dysfunction);
Medication-associated constipation;
Psychiatric disorders;
Inadequate histological material.
While our previous study evaluated the overall distribution of histological phenotypes and included a control group, the present work focused exclusively on the primary clinical cohort to perform an intra-patient comparison of morphological characteristics between the colon and the appendix. The baseline distribution of colonic histological phenotypes was categorized according to a previously established classification model: myopathic, Cajal-cell-deficient, neuropathic, and histologically intact types.

SURGICAL MATERIAL AND TISSUE SAMPLING

Full-thickness fragments of resected colon and appendix were used for morphological analysis. In each case, samples were obtained from all layers of the intestinal wall, including the mucosa, submucosa, muscularis propria, and myenteric plexuses. For the colon, at least three samples from different segments were analyzed in both transverse and longitudinal orientations. The appendix was examined in a same manner as a potential morphological surrogate of a generalized neuromuscular phenotype. The tissue was fixed in 10% buffered formalin, followed by routine paraffin embedding and processing. Serial sections were stained with hematoxylin and eosin. For the assessment of interstitial cells of Cajal, immunohistochemical analysis was performed using CD117 (C-kit), in accordance with a previously validated methodology.

MORPHOLOGICAL ASSESSMENT

Histological evaluation was performed using light microscopy with morphometric analysis. The architectural features of all layers of the intestinal wall were assessed (Table 1).

Table 1. Structure of the semiquantitative model for morphological assessment of the colon according to structural compartments

Histological blocks	Morphological parameters
Mucosa	• Inflammation • Atrophy • Fibrosis of the lamina propria
Submucosa	• Fibrosis • Vascular changes • Edema • Inflammatory infiltration
Muscular layer (muscularis propria)	• Hypertrophy • Atrophy • Fragmentation • Vacuolization • Inter-fascicular fibrosis
Myenteric (intermuscular) plexus	• Number of ganglia • Neuronal dystrophic changes • Hypo-/aganglionic areas • Fibrosis surrounding plexuses
Interstitial cells of Cajal	• Preserved • Moderately reduced • Markedly reduced • Disorganized

Source: compiled by the authors of this study

Each parameter was assessed using a semiquantitative scoring scale:
0 – no alterations;
1 – mild alterations;
2 – moderate alterations;
3 – severe alterations.
For integrated analysis, individual parameters were grouped into the corresponding morphological blocks (mucosal, submucosal, muscular, neural plexus, and interstitial cells of Cajal blocks), followed by calculation of the mean score for each structural block (Mean Block Score). Since the primary parameter "the preservation of interstitial cells of Cajal" was interpreted in the opposite direction (i.e., a higher score indicated better preservation), it was transformed into the parameter reduced preservation of interstitial cells of Cajal by score inversion according to the formula (3 – actual value). To maintain consistent scale directionality for the interstitial cells of Cajal parameters, inverted scores were used for subsequent Mean Block Score calculations. This methodology provided a standardized interpretation across all morphological blocks, whereby higher scores indicated greater pathological severity. Such standardization enabled the construction of an integrated morphological profile for each patient and allowed accurate identification of the dominant histological phenotype.

HISTOLOGICAL CLASSIFICATION

Patients were categorized into following subtypes according to their dominant histopathological block:
myopathic dystrophic;
myopathic inflammatory;
Cajal cell–related (Cajal);
neuropathic;
histologically intact.

Particular emphasis was placed not on the absolute concordance of all morphological parameters between the colon and the appendix, but rather on the agreement of the dominant morphological phenotype, which was considered a potentially more clinically relevant criterion for preoperative stratification.

STUDY ENDPOINTS

PRIMARY ENDPOINT

Concordance of the histological subtype between the appendix and the colon.

Secondary Endpoints

1. Concordance of the dominant morphological phenotype;
2. Correlation of the integrated block scores (Mean Block Scores) between the appendix and the colon;
3. Diagnostic accuracy of the appendix for identifying the Cajal subtype;
4. The potential of the appendix as a preoperative full-thickness morphological surrogate for predicting the dominant histological phenotype of the colon and personalizing the extent of colectomy.

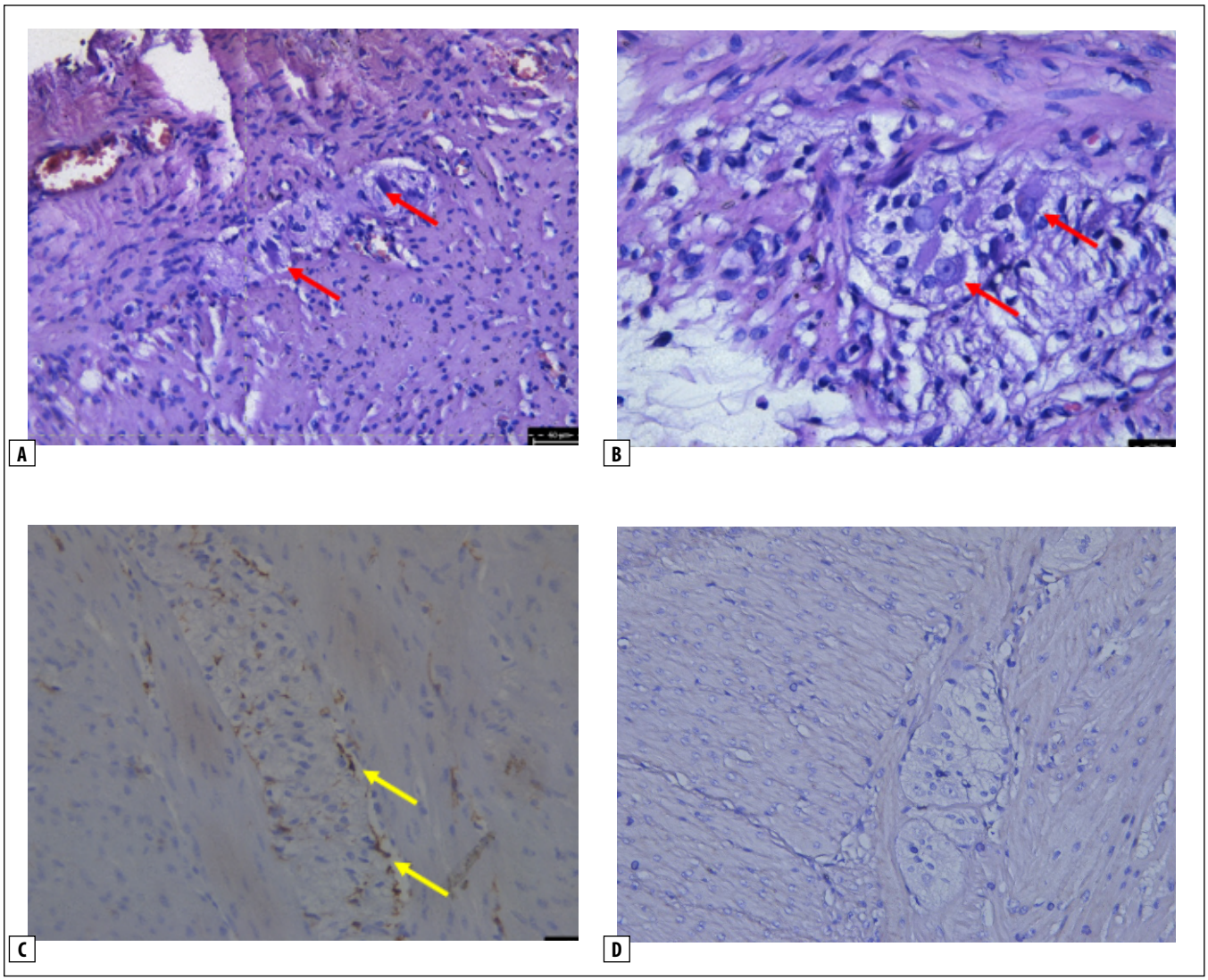


Fig. 1. Neuropathic changes in the colon and appendix (neuropathic subtype of chronic slow-transit constipation).
1A – Colon: degenerative changes of neurons within the myenteric plexus accompanied by hypoganglionosis and disorganization of ganglionic structures (Hematoxylin and eosin staining; magnification×200). 1B – Appendix: similar neurodegenerative alterations of the myenteric plexus with structural distortion of ganglionic elements (Hematoxylin and eosin staining; magnification×200). 1C – Colon: numerous CD117 (c-Kit)-positive interstitial cells of Cajal within the intermuscular space, without evidence of ICC depletion (Immunohistochemistry for CD117 (c-Kit), magnification×200). 1D – Appendix: atrophy and fibrosis of myenteric ganglia (Hematoxylin and eosin staining; magnification ×200)
Picture taken by the authors

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM SPSS Statistics (Version 22.0), including ROC analysis. Descriptive statistics were used to summarize the data, with results presented as mean ± standard deviation (M ± SD) and median with interquartile range (IQR). Distribution normality was assessed using the Shapiro–Wilk test. Intergroup comparisons were assesed using nonparametric methods, including the Mann–Whitney U test and the Kruskal–Wallis test. Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test, as appropriate. Agreement between histological subtypes of colon and appendix was evaluated using Cohen's kappa coefficient, whereas agreement regarding the dominant morphological phenotype was assessed using the weighted kappa coefficient. Spearman's rank correlation analysis was used to study correlations between integrated block scores in the appendix and colon. The diagnostic value of the appendix in predicting the histological subtype of the colon was evaluated by ROC analysis, including calculation of the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A p-value < 0.05 was considered statistically significant.

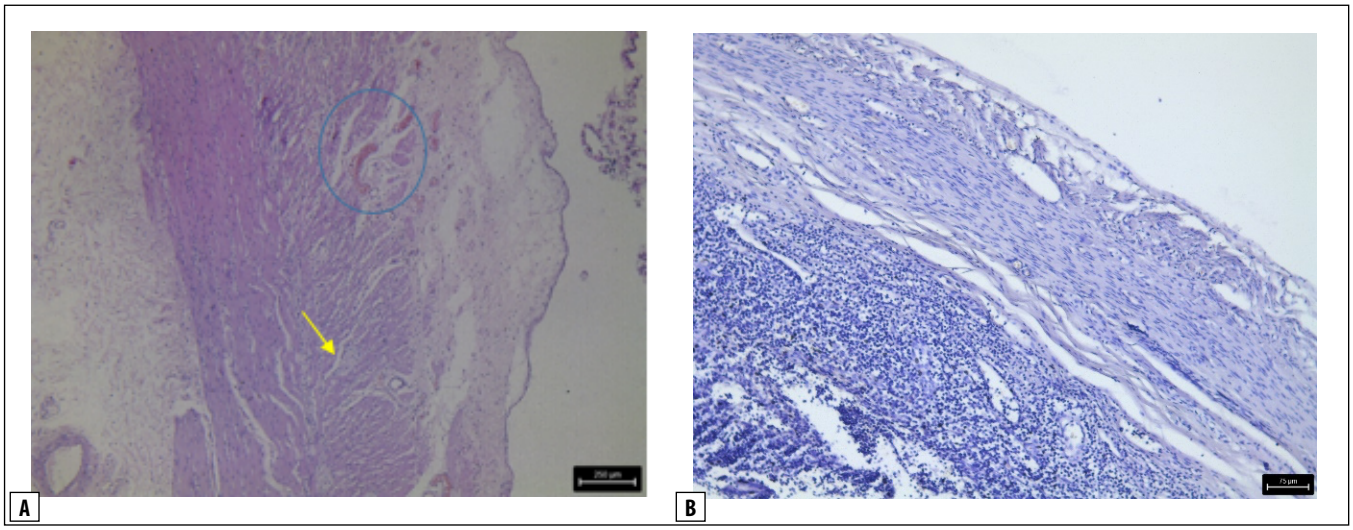


Fig. 2. Myopathic changes in the colon and appendix (myopathic subtype of chronic slow-transit constipation).
2A – Colon: muscularis propria with severe remodeling, disorganization and fragmentation of smooth muscle fibers, intermuscular fibrosis, resulting in to architectural disruption of the circular muscle layer (Hematoxylin and eosin staining; magnification×100). 2B – Appendix: similar degenerative and dystrophic changes of the muscular layer characterized by thinning of smooth muscle structures, focal fibrosis, and heterogeneous organization of muscle fibers (Hematoxylin and eosin staining; magnification ×100). The arrow indicates an area of intermuscular fibrosis and disorganization of smooth muscle fibers
Picture taken by the authors

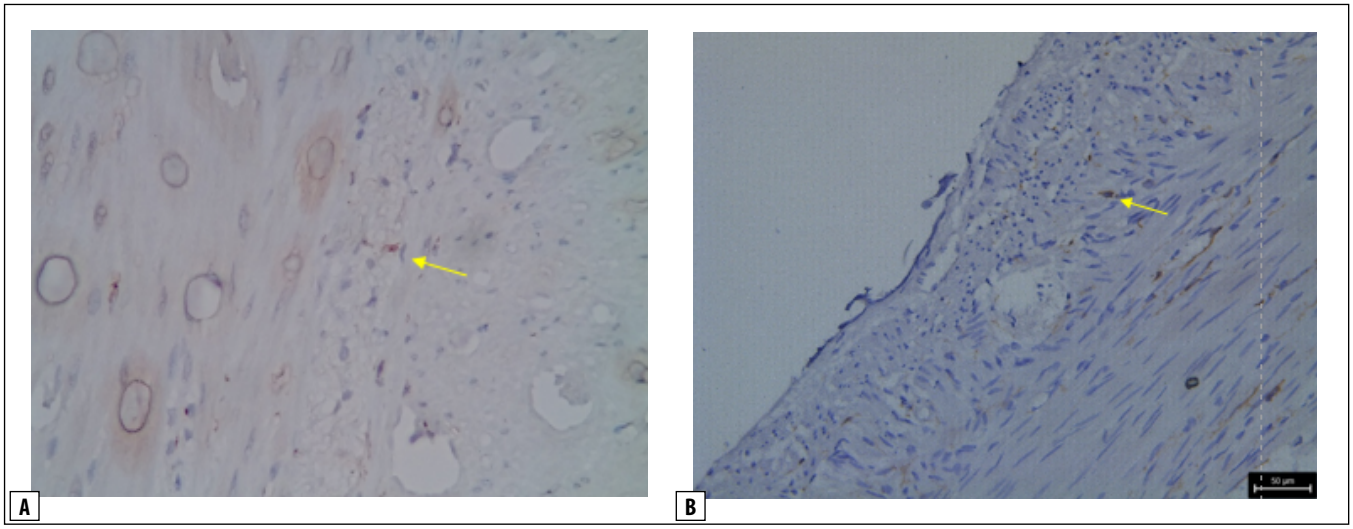


Fig. 3. The Cajal subtype of CSTC. 3A – Colon: isolated spindle-shaped CD117-positive interstitial cells of Cajal in the intermuscular space (Immunohistochemistry for CD117 (c-Kit), magnification×200); 3B – Appendix: similar isolated CD117-positive ICCs in the intermuscular layer (Immunohistochemistry for CD117 (c-Kit), magnification×200). Cajal cells marked by arrows
Picture taken by the authors

METHODOLOGICAL CONCEPT OF THE STUDY

The central hypothesis of this study was that the appendix may serve as an accessible full-thickness morphological surrogate of the dominant histological phenotype of the colon. Such an approach could potentially provide a basis for preoperative stratification of patients with chronic slow-transit constipation and facilitate a personalized approach to determining the optimal extent of colectomy.

ETHICS

This work complies with the principles of the Declaration of Helsinki.

AI STATEMENT

Artificial intelligence tools, including ChatGPT (OpenAI), were used during manuscript preparation exclusively for language editing, stylistic refinement, and prelim-

Table 2. Distribution of Colon Histological Subtypes in Patients with Chronic Slow-Transit Constipation (n = 89)

Histological Subtype	n	%
Myopathic phenotype, overall	46	51.7
Myopathic dystrophic subtype	36	40.4
Myopathic inflammatory subtype	10	11.2
Interstitial cells of Cajal pathology (Cajal subtype)	19	21.3
Neuropathic subtype	17	19.1
Histologically intact subtype	7	7.9
Total	89	100.0

Note. Classification was based on the dominant morphological domain determined through full-thickness histological examination of the colon
Source: compiled by the authors of this study

Table 3. Semiquantitative Characteristics of the Colonic Mucosa and Submucosal Layer According to Histological Subtype of Chronic Slow-Transit Constipation (Mean ± SD)

Morphological Parameter	Histologically Intact (n = 7)	Myopathic Dystrophic (n = 36)	Myopathic Inflammatory (n = 10)	Cajal Subtype (n = 19)	Neuropathic Subtype (n = 17)
Mucosa					
Inflammation	0.1 ± 0.3	0.3 ± 0.4	2.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.5
Atrophy	0.0 ± 0.0	1.1 ± 0.3	0.4 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
Fibrosis of the lamina propria	0.1 ± 0.3	0.9 ± 0.3	1.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Submucosal Layer					
Fibrosis	0.1 ± 0.3	1.0 ± 0.0	1.0 ± 0.0	0.0 ± 0.0	0.4 ± 0.5
Vascular alterations	0.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Edema	0.0 ± 0.0	0.4 ± 0.5	2.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Inflammatory infiltration	0.0 ± 0.0	0.0 ± 0.0	2.3 ± 0.5	0.0 ± 0.0	1.0 ± 0.0

Source: compiled by the authors of this study

Table 4. Semiquantitative characteristics of the muscular layer, myenteric plexus, and interstitial cells of cajal in the colon according to histological subtype of chronic slow-transit constipation (Mean ± SD)

Morphological Parameter	Histologically Intact (n = 7)	Myopathic Dystrophic (n = 36)	Myopathic Inflammatory (n = 10)	Cajal Subtype (n = 19)	Neuropathic Subtype (n = 17)
Muscular Layer					
Hypertrophy	0.0 ± 0.0	1.1 ± 0.3	2.0 ± 0.0	0.2 ± 0.4	0.0 ± 0.0
Atrophy	0.0 ± 0.0	3.0 ± 0.0	1.0 ± 0.0	0.3 ± 0.5	0.0 ± 0.0
Fragmentation	0.0 ± 0.0	2.2 ± 0.4	1.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vacuolization	0.0 ± 0.0	2.8 ± 0.4	1.0 ± 0.0	0.0 ± 0.0	1.2 ± 0.4
Fibrosis between muscle bundles	0.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Myenteric Plexus					
Reduced ganglion density	0.0 ± 0.0	0.2 ± 0.4	0.1 ± 0.3	0.2 ± 0.4	2.7 ± 0.5
Neuronal dystrophic changes	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.5	0.0 ± 0.0	3.0 ± 0.0
Hypo-/aganglionic areas	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.0 ± 0.0
Periplexus fibrosis	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.2 ± 0.4
Interstitial Cells of Cajal					
Reduced preservation of interstitial cells of Cajal[1]	0.0 ± 0.0	0.6 ± 0.5	0.7 ± 0.5	2.7 ± 0.5	0.5 ± 0.5
Moderate reduction	0.0 ± 0.0	0.4 ± 0.5	0.5 ± 0.5	2.0 ± 0.0	0.3 ± 0.5
Severe reduction	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.0 ± 0.0	0.0 ± 0.0
Disorganization	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	3.0 ± 0.0	0.2 ± 0.4

Source: compiled by the authors of this study

inary translation of selected text fragments. Artificial intelligence was not used for data analysis, generation of scientific conclusions, or interpretation of results. All manuscript sections prepared with the assistance of AI were critically reviewed, revised, and approved by the author. All scientific concepts, results, and conclusions represent the author's own intellectual contribution. The author assumes full responsibility for the content of the manuscript.

FRAMEWORK

This work was carried out in accordance with the research plan of the Surgery chair with a Course of Hepatobiliary and Vascular Surgery, Bogomolets National Medical University: «Surgical treatment of chronic disorders of large intestinal transit». State registration number: 0124U001916. The authors received no additional financial support.

RESULTS

89 patients with chronic slow-transit constipation were included in the study. Full-thickness histological examination of colon and appendix specimens was performed in all cases. None of the patients had a history of appendectomy, allowing direct paired comparison of morphological alterations between the colon and the appendix. Histological analysis of the colon demonstrated that the myopathic phenotype was the most prevalent finding, being identified in 46 (51.7%) patients. Among these, the dystrophic myopathic subtype was observed in 36 (40.4%) patients, whereas the inflammatory myopathic subtype was present in 10 (11.2%) patients. Alterations involving the interstitial cells of Cajal were detected in 19 (21.3%) patients, the neuropathic subtype in 17 (19.1%) patients, and a histologically intact phenotype in 7 (7.9%) patients (Table 2).

The myopathic phenotype was the predominant histological pattern, accounting for more than half of the study cohort among those patients after surgery for chronic slow-transit constipation. The dystrophic myopathic subtype was the most common subtype. The Cajal subtype represented approximately one-fifth of all cases. The histologically intact phenotype was the least frequently observed category.

Morphological Characteristics of the Colon According to Histological Subtype Semiquantitative analysis of morphological parameters demonstrated that the different histological subtypes of chronic slow-transit constipation have distinct structural profiles, supporting the pathomorphological validity of the proposed classification (Table 3 and [1] Note. The original parameter, preservation of interstitial cells of Cajal, was transformed into reduced preservation of interstitial cells of Cajal using the formula (3 – actual value) to standardize score direction, where higher scores correspond to more severe pathological alterations.

MORPHOLOGICAL CHARACTERISTICS OF HISTOLOGICAL SUBTYPES

The myopathic inflammatory subtype was characterized by the most severe superficial inflammatory and infiltrative changes. This group demonstrated the highest scores for mucosal inflammation (2.0 ± 0.0), submucosal edema (2.0 ± 0.0), and inflammatory infiltration (2.3 ± 0.5), distinguishing it from all other subtypes. Concurrently, moderate myopathic alterations were observed, including muscular hypertrophy (2.0 ± 0.0), intermuscular fibrosis (2.0 ± 0.0), and less pronounced muscular atrophy (1.0 ± 0.0), indicating the coexistence of inflammatory and tissue-remodeling components. In contrast, the myopathic dystrophic subtype was characterized by predominant degenerative and structural remodeling of the muscular layer with only minimal inflammatory involvement. The highest scores for muscular atrophy (3.0 ± 0.0), vacuolization (2.8 ± 0.4), fragmentation (2.2 ± 0.4), and intermuscular fibrosis (2.0 ± 0.0) were typical for this subtype. Superficial alterations were considerably less severe and were largely limited to mild mucosal atrophy and fibrosis, forming a characteristic dystrophic myopathic phenotype.

The Cajal subtype demonstrated a fundamentally different morphological pattern. Unlike the myopathic forms, the mucosa, submucosa, muscular layer, and neural plexuses generally lacked significant structural abnormalities. However, this group was characterized by the most severe deficiency of interstitial cells of Cajal (ICCs). Severe reduction in ICC density reached 3.0 ± 0.0, disorganization of the ICC network reached 3.0 ± 0.0, and the score for reduced preservation of ICCs was the highest among all subtypes (2.7 ± 0.5). Thus, the Cajal subtype represented a selective ICC-deficient phenotype with minimal involvement of other morphological compartments. Typical microscopic features of the main histological subtypes in colon and appendix are presented in Fig. 1, Fig. 2, Fig. 3.

The neuropathic subtype was characterized by the most severe alterations within the myenteric plexus. This group demonstrated the highest scores for neuronal dystrophy (3.0 ± 0.0), hypo-/aganglionic areas (3.0 ± 0.0), reduced ganglion density (2.7 ± 0.5), and periplexus fibrosis (2.2 ± 0.4). In contrast, superficial changes and structural remodeling of the muscular layer were substantially less pronounced, supporting predomi-

Table 5. Integrated block-based characteristics of colonic histological subtypes in patients with chronic slow-transit constipation (Mean ± SD)

Integrated Morphological Block	Histologically Intact (n = 7)	Myopathic Dystrophic (n = 36)	Myopathic Inflammatory (n = 10)	Cajal Subtype (n = 19)	Neuropathic Subtype (n = 17)
Mucosal score	0.07 ± 0.18	0.77 ± 0.33	1.13 ± 0.17	0.00 ± 0.00	0.13 ± 0.17
Submucosal score	0.04 ± 0.10	2.40 ± 0.29	6.30 ± 0.48	0.00 ± 0.00	1.40 ± 0.32
Muscular score	0.00 ± 0.00	10.11 ± 0.32	7.00 ± 0.00	0.53 ± 0.22	1.24 ± 0.44
Neuronal score	0.00 ± 0.00	0.05 ± 0.14	0.10 ± 0.18	0.05 ± 0.11	13.65 ± 1.17
Cajal cell pathology score	0.00 ± 0.00	1.00 ± 0.41	1.20 ± 0.44	10.70 ± 0.87	1.00 ± 0.36
Total histological score	0.11 ± 0.21	14.33 ± 0.74	15.73 ± 0.82	11.28 ± 0.96	17.42 ± 1.41

Source: compiled by the authors of this study

Table 6. Overall concordance of histological phenotype between the colon and the appendix (ТК – colon; АП – appendix)

Measure of concordance	Value
Exact histological subtype match	98.9% (88/89 patients)
Concordance of dominant morphological phenotype	100% (89/89 patients)
Cohen's kappa coefficient (exact subtype match)	0.985
Weighted kappa coefficient (dominant phenotype)	1.00

Source: compiled by the authors of this study

Table 7. Correlation of Integrated Morphological Blocks Between the Appendix and the Colon

Integrated Morphological Block	Spearman's correlation coefficient (r)	p-value
Mucosal score	0.81	<0.001
Submucosal score	0.84	<0.001
Muscular score	0.93	<0.001
Neural plexus score	0.96	<0.001
Cajal cell pathology score	1.00	<0.001

Source: compiled by the authors of this study

Table 8. Diagnostic efficacy of Appendix Histology in Predicting Colonic Histological Subtype.

Diagnostic parameter	Cajal subtype	Neuropathic subtype	Myopathic subtype (overall)
Sensitivity (%)	100.0	94.1	95.7
Specificity (%)	100.0	98.2	96.5
Positive predictive value (PPV, %)	100.0	94.1	97.8
Negative predictive value (NPV, %)	100.0	98.2	93.2
Overall accuracy (%)	100.0	97.1	96.1

Source: compiled by the authors of this study

Table 9. ROC Characteristics of Integrated Morphological Blocks of the Appendix for Predicting the Dominant Histological Colon Subtype

Target colonic histological subtype	Primary appendiceal predictor	AUC (95% CI)	Cut-off	Sensitivity, %	Specificity, %
Cajal subtype	Cajal cell pathology score	1.00 (0.96–1.00)	≥8.5	100.0	100.0
Neuropathic subtype	Neural plexus score	0.98 (0.94–1.00)	≥9.5	94.1	98.2
Myopathic subtype (overall)	Muscular score	0.96 (0.91–0.99)	≥6.5	95.7	96.5

Source: compiled by the authors of this study

nant involvement of the enteric nervous system as the principal pathogenetic mechanism. The histologically intact subtype was characterized by minimal or absent alterations across all structural compartments, including the mucosa, muscular layer, neural plexuses, and interstitial cells of Cajal and therefore represented the

morphologically least affected phenotype within the study cohort. Overall, the findings indicate that each histological subtype has a distinct dominant structural pattern: a muscular pattern in the myopathic subtypes, neural plexus pathology in the neuropathic subtype, and selective depletion of interstitial cells of Cajal in the Cajal subtype. Typical microscopic features of the main histological subtypes in colon and appendix are presented in Fig. 1, Fig. 2, Fig. 3.

These findings support the validity of not only a categorical patient classification but also the subsequent application of a quantitative integrated block-based model for predicting the dominant morphological phenotype.

INTEGRATED HISTOLOGICAL CHARACTERIZATION OF COLONIC HISTOLOGICAL SUBTYPES ACCORDING TO STRUCTURAL HISTOLOGICAL BLOCKS

To summarize semiquantitative morphological characteristics, individual parameters were integrated into five principal structural blocks: mucosal, submucosal, muscular, neural, and interstitial cells of Cajal (Cajal) blocks. Analysis of the cumulative integrated block scores confirmed that the proposed histological subtypes are characterized not only by distinct individual morphological features but also by fundamentally different pathomorphological architectures (Table 5).

The myopathic dystrophic subtype was characterized by the predominance of the muscular block, which demonstrated one of the highest integrated values among all subtypes (10.11 ± 0.32). This finding confirms that structural degenerative involvement of the muscular layer represents its principal morphological feature. At the same time, the mucosal (0.77 ± 0.33) and neuronal (0.05 ± 0.14) blocks remained minimally altered, further emphasizing the selective nature of muscular remodeling.

The myopathic inflammatory subtype also demonstrated a high muscular component (7.00 ± 0.00); however, in contrast to the dystrophic variant, it was accompanied by markedly higher mucosal and submucosal block scores (1.13 ± 0.17 and 6.30 ± 0.48, respectively). The combination of muscular remodeling with prominent inflammatory and infiltrative changes in the superficial layers defined a distinct pathogenetic profile of this subtype.

The Cajal subtype demonstrated a fundamentally other integrated architectural pattern: in the presence of minimal alterations in the mucosal, submucosal, muscular, and neuronal blocks, it was characterized by a dominant Cajal cell pathology score (10.70 ± 0.87). So, despite a relatively lower overall morphological burden compared to the neuropathic variant, this subtype has a highly specific pathogenetic mechanism associated with selective impairment of the interstitial cells of Cajal (ICC).

The neuropathic subtype had the highest total histological score (17.42 ± 1.41) among all variants, demonstrating the most severe structural remodeling. The neuronal block was predominant (13.65 ± 1.17), whereas the remaining structural components were relatively less affected. Thus, a neurodegenerative component represents the principal morphological determinant of this subtype.

The histologically intact subtype was characterized by the lowest values across all blocks (total histological score: 0.11 ± 0.21), confirming the absence of significant structural remodeling despite the presence of the clinical syndrome of slow-transit constipation.

Data from the integrated block scores indicated that the total morphological burden does not always mirror the clinical severity of specific subtypes. The neuropathic variant had the highest total structural score, the Cajal subtype after standardized evaluation of ICC deficiency showed a markedly high block-specific pathological burden, underscoring its morphological selectivity. These findings prompted further evaluation of not only the total morphological burden but also the dominant histological phenotype, highlighting it as a potentially more clinically relevant criterion. Overall, the integrated block-based assessment confirmed clearly distinct morphological architectures among histological subtypes. The myopathic dystrophic variant was characterized by the highest muscular score (10.11 ± 0.32), the myopathic inflammatory subtype by a combination of elevated submucosal and muscular scores (6.30 ± 0.48 and 7.00 ± 0.00, respectively), the Cajal subtype by selective predominance of the Cajal cell pathology score (10.70 ± 0.87), and the neuropathic subtype by the highest neuronal score (13.65 ± 1.17) and the greatest total histological score (17.42 ± 1.41).

Concordance of Histological Characteristics Between the Appendix and the Colon

Comparative analysis of histological characteristics of the appendix and the colon demonstrated an exceptionally high level of concordance between dominant morphological phenotypes (Table 6, Table 7).

Notes. *Exact histological subtype match* was defined as complete concordance of the classification subtype between the colon and the appendix. *Dominant morphological phenotype* referred to concordance of the principal pathogenetic block regardless of regional variations in the severity of morphological changes. *PPV (positive predictive value)* represents the probability of

confirming the corresponding colonic subtype when the appendiceal histological result is positive. *NPV (negative predictive value)* represents the probability of excluding the corresponding colonic subtype when the appendiceal histological result is negative. Overall, exact match of the histological subtype between the appendix and the colon was observed in 98.9% of cases (88 of 89 patients), whereas concordance of the dominant pathogenetic phenotype reached 100% (89 of 89 patients). Cohen's kappa coefficient for exact subtype match was 0.985, indicating almost perfect categorical concordance, while the weighted kappa coefficient for dominant phenotype was 1.00. Correlation analysis of the integrated morphological blocks between the appendix and the colon further confirmed the high reproducibility of the histological profile. The highest level of concordance was observed for the Cajal cell pathology score ($r = 1.00$; $p < 0.001$), which was important for the identification of the Cajal subtype. Very strong correlations were also found for the neural plexus block ($r = 0.96$; $p < 0.001$) and the muscular block ($r = 0.93$; $p < 0.001$), whereas the mucosal ($r = 0.81$; $p < 0.001$) and submucosal ($r = 0.84$; $p < 0.001$) blocks showed greater variability. These findings suggest that superficial and inflammatory-reactive changes may vary regionally, while the underlying structural pattern remains preserved.

The Cajal subtype is the most clinically relevant phenotype. In all patients with interstitial Cajal cell deficiency in the colon, the same phenotype was confirmed in the appendix, resulting in 100% sensitivity, 100% specificity, and 100% overall diagnostic accuracy for this morphological surrogate. Thus, within the studied cohort, the appendix demonstrated complete concordance in the identification of the Cajal phenotype. A very high level of diagnostic efficacy was also observed for the neuropathic subtype, with a sensitivity of 94.1%, specificity of 98.2%, and overall accuracy of 97.1%. Diagnostic accuracy remained high for the myopathic subtypes (96.1%); however, this group showed the greatest regional variation in the intensity of some morphological parameters. Specifically, the inflammatory-infiltrative component was less pronounced in the appendix in cases of the myopathic inflammatory subtype, whereas degenerative changes tended to be somewhat more pronounced in the appendix in the myopathic dystrophic subtype. Despite these differences, the dominant muscular phenotype remained stable. These findings indicate that the appendix does not always necessarily reproduce the absolute severity of all morphological alterations present in the colon; however, it almost perfectly reflects the dominant histological phenotype. This is critical because preoperative stratification and the choice of colectomy type depend on identifying the primary pathogenetic mechanism, rather than achieving an absolute concordance of all histological features. Therefore, full-thickness histological examination of the appendix may be considered a highly accurate phenotype-preserving surrogate marker of colonic pathology. These findings provide a basis for a stepwise histology-guided surgical strategy, in which laparoscopic appendectomy followed by morphological assessment may serve as a diagnostic tool for personalizing the extent of colectomy in patients with chronic slow-transit constipation.

ROC analysis of appendiceal histology predictive value for the dominant colonic histological subtype

To quantify the predictive value of the appendix as a preoperative morphological surrogate, a ROC analysis of the main integrated morphological blocks was performed to predict the dominant colonic histological phenotype. (Table 9).

ROC analysis revealed that the appendiceal ICC score perfectly predicted the colonic Cajal subtype (AUC = 1.00). A cutoff of ≥8.5 yielded 100.0% sensitivity and specificity, demonstrating total diagnostic reproducibility of this phenotype within the cohort.

For the neuropathic subtype, the most informative predictor was the appendiceal neural plexus score (AUC = 0.98), demonstrating exceptionally high predictive accuracy. An optimal cut-off value of ≥9.5 yielded a sensitivity of 94.1% and a specificity of 98.2%.

The myopathic subtypes exhibited somewhat greater morphological variability; nevertheless, the appendiceal muscular score remained a highly accurate predictor (AUC = 0.96). Appendix reliably represents the dominant myopathic phenotype of the colon despite regional differences in the severity of individual morphological alterations, as evidenced by this data.

The ROC analysis demonstrated different predictive value of the appendix for all morphological subtypes. The highest diagnostic accuracy was observed for the Cajal subtype: selective depletion of interstitial Cajal cells has complete morphological concordance between the appendix and the colon. The last is clinically pivotal, as the Cajal phenotype is associated with severe functional impairment, potentially representing the subgroup most likely to benefit from extensive surgery. Consequently, ROC analysis validated appendiceal histology as a diagnostic tool, transforming descriptive morphology into a clinically relevant, phenotype-guided preoperative stratification framework.

DISCUSSION

Chronic slow-transit constipation is a heterogeneous syndrome rather than a single nosological pathology,

with impaired colonic motility arising from distinct myopathic, neuropathic, or interstitial cell of Cajal (ICC)-deficient mechanisms. [11,13,16–19]. Contemporary concepts of gastrointestinal neuromuscular pathology, including the London Classification of Gastrointestinal Neuromuscular Pathology, emphasize the critical importance of structured full-thickness morphological assessment of the bowel wall for understanding the pathogenesis of severe motility disorders [7]. However, routine preoperative full-thickness colonic stratification remains unavailable, leaving a gap between the pathomorphological substrate and surgical decision-making. Importantly, the morphological assessment employed in the present study extended beyond a purely descriptive approach. Integrating individual parameters into a standardized, semiquantitative block model (mucosal, submucosal, muscular, neural, and ICC domains) shifted the focus from fragmented descriptive analysis to systematic phenotypic characterization. This foundational methodological framework enabled both the identification of pathological changes and the precise quantification of each patient's dominant pathogenetic component. The proposed semiquantitative model transformed histological assessment from a predominantly descriptive tool into a stratification-oriented methodology. The present findings confirm that patients with chronic slow-transit constipation do not represent a morphologically homogeneous population. The myopathic dystrophic subtype was characterized by predominance of the muscular block (10.11 ± 0.32), the myopathic inflammatory subtype by a combination of elevated muscular (7.00 ± 0.00) and submucosal (6.30 ± 0.48) components, the Cajal subtype by selective predominance of Cajal cell pathology (10.70 ± 0.87), whereas the neuropathic subtype demonstrated the highest neuronal score (13.65 ± 1.17) and the greatest overall histological score (17.42 ± 1.41). As a consequence, despite similar clinical manifestations, the structural basis of disease may differ fundamentally among patients. Importantly, these findings have direct clinical utility, as post-colectomy outcomes for slow-transit constipation vary widely, and standard criteria for optimal extent of resection remain unestablished. [8,20–22]. Particular attention should be paid to the Cajal subtype, which in our study was characterized by the most severe selective deficiency of interstitial Cajal cells (Cajal cell pathology score: 10.70 ± 0.87), with minimal alterations in the other morphological blocks. These findings align with the observations of He et al. [17] and Wedel et al. [18]. [16], who demonstrated the role of ICC deficiency in the pathogenesis of severe slow-transit constipation. However, these concepts are further extended by the current data, which suggest that ICC depletion constitutes a distinct dominant histological phenotype of independent clinical value. A central conceptual finding of the present study was the exceptionally high concordance of histological phenotypes between the appendix and the colon. Exact match of histological subtype reached 98.9% (88 of 89 patients), whereas concordance of the dominant morphological phenotype was 100% (89 of 89 patients), with Cohen's kappa of 0.985 and weighted kappa of 1.00, respectively. Such a level of concordance fundamentally expands current perspectives regarding the potential role of the appendix in the diagnostic algorithm of chronic slow-transit constipation. Analysis of the integrated morphological blocks further comfirmed this observation. Correlations between the appendix and the colon reached $r = 0.93$ for the muscular block, $r = 0.96$ for the neuronal block, and $r = 1.00$ for the Cajal cell pathology block ($p < 0.001$ for all comparisons). The latter finding is particularly important, as every patient with a Cajal colon subtype demonstrated the same phenotype in the appendix. Thus, within the present cohort, the appendix showed complete diagnostic concordance for the identification of the ICC-deficient phenotype. This concordance is potentially explained not only by the functional features but also by the common embryological lineage of the appendix and colon. The appendix arises from the cecal segment of the midgut and develops within the same morphogenetic part as the proximal colon, retaining a similar overall wall architecture, enteric nervous system organization, and mesenchymal–epithelial interactions [15,23]. Although this does not imply absolute identity of all regional histological alterations, it provides a biological explanation for the dominant phenotype. The appendix may therefore function not as an anatomical replica of the colon but rather as a phenotype-predicting full-thickness morphological surrogate. Importantly, the appendix do not always mirror the exact severity of all histological alterations in the colon. The mucosal ($r = 0.81$) and submucosal ($r = 0.84$) blocks showed the lowest correlation, likely due to regional differences in superficial inflammatory-reactive changes. M ethodologically, the clinical value of appendiceal histology depends not on mirroring isolated morphological details, but on capturing the dominant pathogenetic phenotype. The present findings also allow to separate overall morphological burden and potential functional severity. Although the neuropathic subtype had the highest total histological score (17.42 ± 1.41), this does not necessarily means the greatest treatment resistance. Conversely, despite a lower overall histological score (11.28 ± 0.96), the Cajal subtype may be functionally more critical because of selective impairment of gastrointestinal motor coordination key mechanism.

Consequently, the optimal extent of colectomy appears to be depend on the dominant phenotype rather than the overall degree of structural damage. Practically, these findings provide a framework for histology-guided surgical stratification. Theoretically, laparoscopic appendectomy followed by full-thickness histological evaluation could serve as an additional diagnostic step in complex cases of chronic slow-transit constipation where the choice between segmental, subtotal, and total colectomy remains uncertain. This approach does not replace standart clinical and functional diagnostics but improves it with morphological data.

This study has several limitations. The investigation was carried out in a single-center cohort of 89 patients without external validation. The proposed semiquantitative scoring system requires further evaluation with respect to interobserver reproducibility. In addition, the concept of a separate preoperative appendectomy as a diagnostic procedure aquires prospective assessment of its risk–benefit profile and its impact on clinical outcomes.

In summary, the present study not only confirms the morphological heterogeneity of chronic slow-transit constipation but also demonstrates that a standardized semiquantitative block-based model enables a transition from descriptive histology to phenotype-oriented morphological stratification. Appendix serves as a full-thickness morphological surrogate for the dominant histological subtype of the colon. This concept offers high clinical value by defining the Cajal subtype, which directly guides personalized colectomy extent. Once validated prospectively, these data will support a novel phenotype-guided paradigm in the surgical treatment of chronic slow-transit constipation.

CONCLUSIONS

Chronic slow-transit constipation is characterized by substantial morphological heterogeneity, with the formation of myopathic, neuropathic, and ICC-deficient phenotypes. The appendix demonstrates exceptionally high concordance with the dominant histological phenotype of the colon and may therefore be considered a phenotype-predicting full-thickness morphological surrogate. These findings establish a framework for the further phenotype-guided approach to personalize the extent of colectomy in patients with chronic slow-transit constipation.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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RECEIVED: 10.04.2026
ACCEPTED: 28.08.2026

CREATIVE COMMONS 4.0