

# Histological Predictors of Anastomotic Stenosis in Esophageal Substitution Surgery

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**Objective:** To evaluate histopathological markers of inflammation and tissue repair in esophageal specimens obtained during substitution surgery and determine their association with postoperative anastomotic stenosis.

**Design:** Retrospective cross-sectional study.

**Setting:** Tertiary care referral center (Clínica de Tracto Digestivo Superior, Hospital General de México “Dr. Eduardo Liceaga”).

**Participants:** Sixteen adults undergoing esophageal substitution for benign disease between January 2012 and January 2022. Inclusion required complete clinical records and native esophageal histology; cases with malignancy or missing histology were excluded.

**Methods:** Archived slides from the proximal esophageal margin were reviewed with hematoxylin and eosin and Masson’s trichrome. A semi-quantitative score assessed neutrophilic infiltration, lymphocytic infiltration, collagen deposition, and granulation tissue across mucosa, submucosa, and muscularis (range 0–18), classifying profiles as low risk ( $\leq 15$ ) or high risk ( $\geq 16$ ). Patients were grouped by presence (CEA) or absence (SEA) of postoperative stenosis. Statistical comparisons used Fisher’s exact test and Mann–Whitney U, with medians (IQR) and exact p-values.

**Results:** Median total histological scores were higher in CEA than SEA (18 [17–18] vs 12 [9–15];  $P=0.014$ ). All stenosis cases were high-risk, whereas 92.3% of non-stenosis cases were low-risk ( $P=0.007$ ). Individual inflammatory markers were not statistically different between groups; however, collagen deposition and granulation tissue appeared more severe among CEA patients. No meaningful differences in demographic or operative variables were observed.

**Conclusion:** In this exploratory study, a composite histopathological score identified patients at increased risk of postoperative anastomotic stenosis. The approach may support risk stratification and surveillance in gastrointestinal reconstructive surgery and warrants external validation.

**Keywords:** Anastomotic stenosis; Collagen deposition; Esophageal substitution; Fibrosis; Gastrointestinal reconstruction; Histopathology; Inflammation; Surgical complications

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Esophageal substitution surgery is a complex procedure undertaken for advanced esophageal dysfunction—including end-stage achalasia, refractory peptic strictures, and caustic injury. Despite advances in technique and perioperative care, anastomotic stenosis (anastomotic stricture) remains a frequent and challenging complication, with incidences reported between 4% and 46% across specialized centers.<sup>1,2</sup> Resultant dysphagia, repeated endoscopic dilations, and prolonged follow-up substantially affect quality of life and resource use.<sup>3</sup>

Among available reconstructions, gastric pull-up is generally preferred owing to operative efficiency and robust vascularity.<sup>4,5</sup> When gastric viability is limited—such as after prior surgery or extensive corrosive injury—colonic interposition offers a reliable alternative.<sup>6,7</sup> Nevertheless, complications including anastomotic leakage, infection, and especially stenosis persist.<sup>8,9</sup> Increasing evidence suggests tissue-level healing dynamics, rather than technical variation alone, drive downstream stricture formation.

Postoperative healing involves overlapping phases of acute and chronic inflammation, granulation tissue formation, and extracellular-matrix remodeling. Dysregulated responses, marked by persistent neutrophilic and lymphocytic infiltration, exuberant granulation tissue, and excess collagen deposition promote fibroproliferative remodeling and progressive luminal narrowing.<sup>10</sup> Yet routine histopathology at the anastomotic margins typically focuses on excluding malignancy or dysplasia, and there is no standardized method to semi-quantitatively score inflammation or fibrosis in this context.<sup>11,12</sup>

Other gastrointestinal disorders (e.g., Crohn's disease, chronic gastritis) routinely incorporate biopsy-based scoring systems into diagnostic and therapeutic algorithms,<sup>13,14</sup> illustrating how structured histopathology can inform management and predict complications.

Building on these precedents, we adapted published frameworks to esophageal substitution surgery, specifically the chronic gastritis classification by Du et al.<sup>15</sup> and experimental esophageal-injury models by Cevik et al.<sup>16</sup>, focusing on four domains: neutrophilic infiltration, lymphocytic infiltration, collagen deposition, and granulation tissue across mucosa, submucosa, and muscularis.

We hypothesized higher composite histopathological scores, particularly those reflecting extensive fibrosis together with sustained inflammation, would be associated with the subsequent development of anastomotic stenosis. Consistent with the study's scale, our objective was to evaluate the clinical coherence and feasibility of a semi-quantitative, clinically actionable scoring framework for postoperative risk stratification, acknowledging that findings are exploratory and require external validation.

## Methods

### *Study Design*

This retrospective cross-sectional study was conducted at a tertiary referral center and used archived histological slides from esophageal substitution procedures performed between January 2012 and January 2022, together with corresponding retrospective clinical data.

### *Ethical Considerations*

The protocol was approved by the Research and Ethics Committee of the Hospital General de México (DI/22/501/05/41). In accordance with the General Health Law for Health Research in Mexico and CIOMS guidelines, the study was classified as risk-free and exempt from informed consent, because only anonymized archival histopathology and retrospective clinical data were used. Patient confidentiality and data protection were rigorously maintained.

### *Study Population and Sample Size*

A target sample size of 36 was estimated from a reported stenosis prevalence of 46% ( $\alpha=0.05$ , power=0.91, effect size=0.26).<sup>2</sup> Because the available archive yielded 16 eligible cases, analyses were treated as exploratory and intended to estimate effect direction for future validation.

### *Histological Slide Preparation and Evaluation*

Slides from the proximal esophageal margin were retrieved and stained with hematoxylin and eosin (H&E) for inflammation and Masson's trichrome for fibrosis/repair. Two observers (lead investigator and senior histopathologist) reviewed slides independently using a Zeiss Axio Lab A.1 microscope with digital imaging; discrepancies were resolved by consensus.

### *Histopathological Scoring System*

A semi-quantitative composite score, adapted from Du et al.<sup>14</sup> (chronic gastritis classification) and Cevik et al.<sup>15</sup> (experimental esophageal injury), evaluated four domains: neutrophilic infiltration (IN), lymphocytic infiltration (IL), granulation tissue (TG), and collagen deposition (DC). Each domain was graded across mucosa, submucosa, and muscularis, yielding a 0–18 total score. For descriptive risk strata, profiles were categorized as low-risk ( $\leq 15$ ) or high-risk ( $\geq 16$ ) according to the composite score; patients were grouped by the presence (CEA) or absence (SEA) of postoperative stenosis.

### *Statistical Analysis*

Data were managed in Microsoft Excel and analyzed in SPSS v29. Continuous variables are summarized as median (IQR) and categorical variables as n (%). Bivariate comparisons used Fisher's exact test for categorical data and the Mann–Whitney U test for continuous data. We report exact *P* values and emphasize estimate precision and clinical context rather than dichotomous significance testing; all tests were two-sided with  $\alpha=0.05$ .

**Table 1. Demographic, Etiological, and Perioperative Characteristics of Patients Undergoing Esophageal Substitution Surgery**

Variable	SEA Group (n = 13)	CEA Group (n = 3)	Total (n = 16)	P value
Sex				0.931 <sup>a</sup>
Female	4 (30.8%)	1 (33.3%)	5 (31.3%)	
Male	9 (69.2%)	2 (66.7%)	11 (68.7%)	
Age (years)	47.0 ± 16.7	34.6 ± 13.2	44.6 ± 16.4	0.226 <sup>b</sup>
Body Mass Index (kg/m <sup>2</sup> )	21.7 ± 2.3	21.4 ± 0.89	21.7 ± 2.2	0.981 <sup>b</sup>
Etiology				0.297 <sup>a</sup>
Caustic ingestion	5 (38.5%)	3 (100%)	8 (50%)	
Peptic stricture	4 (30.8%)	0	4 (25%)	
Achalasia	2 (15.4%)	0	2 (12.5%)	
Esophageal perforation	2 (14.4%)	0	2 (12.5%)	—
Preoperative Albumin (g/dL)	3.7 ± 0.6	4.0 ± 0.5	3.8 ± 0.6	0.505 <sup>b</sup>
Graft Used				0.375 <sup>a</sup>
Colon	5 (38.5%)	2 (66.7%)	7 (43.8%)	
Stomach	8 (61.5%)	1 (33.3%)	9 (56.3%)	
Anastomosis Type				0.522 <sup>a</sup>
Manual	6 (46.2%)	2 (66.7%)	8 (50%)	
Mechanical	7 (53.8%)	1 (33.3%)	8 (50%)	

<sup>a</sup>Fisher's exact

<sup>b</sup>Mann-Whitney U

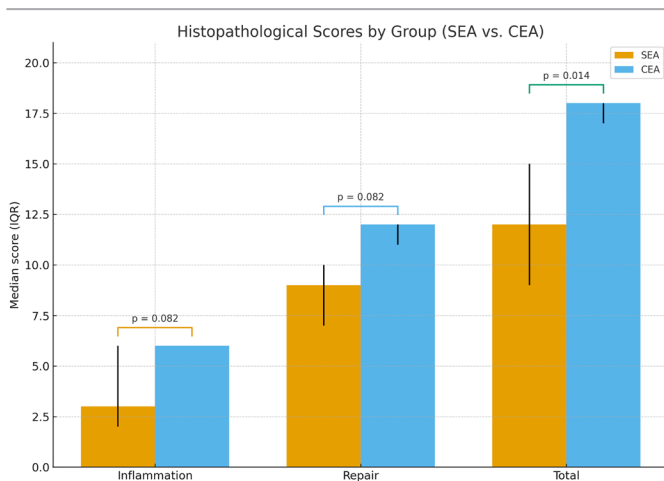
Abbreviations: SEA = without anastomotic stenosis; CEA = with anastomotic stenosis

## Results

### Demographic and Clinical Characteristics

There were 16 patients included in the study; 13 (81.2%) had no postoperative anastomotic stenosis (SEA) and 3 (18.8%)

developed stenosis (CEA). Baseline demographic and operative characteristics were similar between groups (Table 1). The most common indication for reconstruction was caustic injury, followed by peptic strictures and achalasia. Both gastric pull-up and colonic interposition were performed, and manual versus mechanical anastomosis was evenly distributed, with no meaningful between-group differences.



**Figure 1. Histopathological scores by group (SEA vs. CEA).** Bars display medians with interquartile ranges (IQR) for the inflammation, repair, and total composite scores. Patients with anastomotic stenosis (CEA) showed higher total scores than those without (SEA) ( $P=0.014$ ), whereas inflammation and repair comparisons were not statistically significant (both  $P=0.082$ ). SEA = without anastomotic stenosis; CEA = with anastomotic stenosis.

### Histopathological Patterns

Across domains, inflammation and repair scores were higher among CEA patients. Differences in neutrophilic and lymphocytic infiltration did not reach statistical significance ( $P=0.158$  and  $P=0.432$ , respectively). Collagen deposition was present in 93.8% of specimens, and granulation tissue was more frequently severe in CEA cases. The total composite histopathological score was higher in CEA than in SEA (median 18 [17–18] vs 12 [9–15];  $P=0.014$ ) (Table 2).

### Visual Summary and Risk Classification

Histopathological classification based on total score stratification showed that all CEA cases were high-risk ( $\geq 16$ ), while 92.3% of SEA were low-risk ( $\leq 15$ );  $P=0.007$  (Fisher's exact). Figure 1 summarizes group distributions for inflammation, repair, and total scores (medians with IQR), showing higher total scores among CEA patients. Figures 2–5 provide representative gross and histologic images spanning low- and high-risk profiles.

**Table 2. Histopathological Findings and Total Inflammation/Repair Scores in SEA and CEA Groups**

Variable	SEA Group (n = 13)	CEA Group (n = 3)	Total (n = 16)	P value
Neutrophilic Infiltrate				0.158 <sup>a</sup>
Normal	7 (53.8%)	0	7 (43.8%)	
Mild	1 (7.7%)	0	1 (6.3%)	
Severe	5 (38.5%)	3 (100%)	8 (50.0%)	
Lymphocytic Infiltrate				0.432 <sup>a</sup>
Normal	3 (23.1%)	0	3 (18.8%)	
Mild	2 (15.4%)	0	2 (12.5%)	
Severe	8 (61.5%)	3 (100%)	11 (68.8%)	
Collagen Deposition				0.620 <sup>a</sup>
Absent	1 (7.7%)	0	1 (6.3%)	
Present	12 (92.3%)	3 (100%)	15 (93.8%)	
Granulation Tissue				0.573 <sup>a</sup>
Absent	4 (30.8%)	0	4 (25%)	
Mild	1 (7.7%)	0	1 (6.3%)	
Moderate	4 (30.8%)	1 (33.3%)	5 (31.3%)	
Severe	4 (30.8%)	2 (66.7%)	6 (37.5%)	
Inflammation Score (Median, IQR)	3 (2–6)	6 (6–6)	4.5 (2.5–6)	0.082 <sup>b</sup>
Repair Score (Median, IQR)	9 (7–10)	12 (11–12)	9 (7.5–12)	0.082 <sup>b</sup>
Total Score (Median, IQR)	12 (9–15)	18 (17–18)	13.6 (9.5–16)	0.014 <sup>b</sup>
Histopathological Pattern				0.007 <sup>c</sup>
Low Risk ( $\leq 15$ pts)	12 (92.3%)	0	12 (75%)	
High Risk ( $\geq 16$ pts)	1 (7.7%)	3 (100%)	4 (25%)	

<sup>a</sup>Chi-square test<sup>b</sup>Mann–Whitney U test<sup>c</sup>Fisher's exact test

Abbreviations: SEA = without anastomotic stenosis; CEA = with anastomotic stenosis; IQR = interquartile range.

### Postoperative Outcomes

Early complications ( $\leq 30$  days) occurred in 56.3% of patients (Table 3). No statistically significant association was observed between anastomotic leak and subsequent stenosis; however,

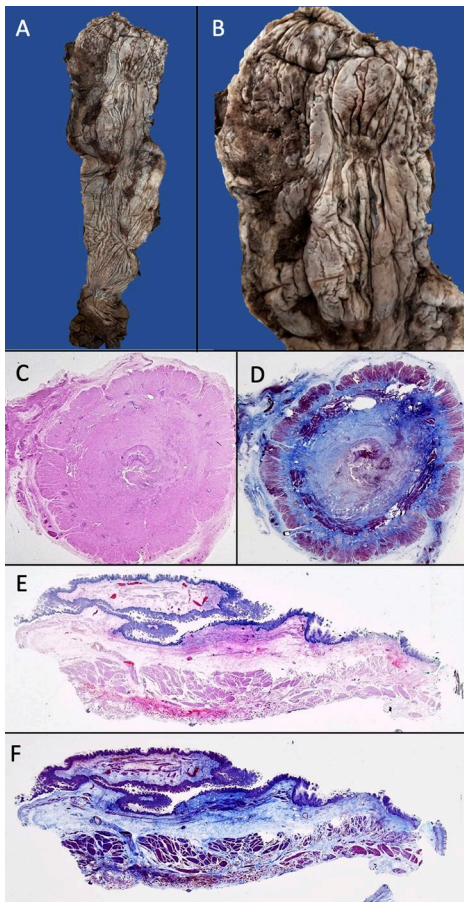
the point estimate (OR 4.5; 95% CI 0.31–65.2) suggests a possible relationship that warrants evaluation in larger cohorts. Time to stenosis among CEA patients was 3 months (IQR 3–4).

**Table 3. Postoperative Complications and Outcomes in SEA and CEA Groups**

Variable	SEA Group (n = 13)	CEA Group (n = 3)	Total (n = 16)	P value
Early Complication ( $\leq 30$ days)	6 (46.2%)	3 (100%)	9 (56.3%)	0.090 <sup>a</sup>
Time to Stenosis (months)	—	3 (3–4)	—	—
Anastomotic Leak				0.247 <sup>1</sup> OR 4.5 (CI: 0.31–65.2)
No	9 (69.2%)	1 (33.3%)	10 (62.5%)	
Yes	4 (30.8%)	2 (66.7%)	6 (37.5%)	
Time to Leak (days)	6 $\pm$ 3.6	16 $\pm$ 8.5	8.8 $\pm$ 2.9	0.063 <sup>b</sup>
Follow-up Duration (months)	10 $\pm$ 8.3	17.3 $\pm$ 2.0	11.4 $\pm$ 8.0	0.850 <sup>b</sup>
Vital Status				0.142 <sup>a</sup>
Alive	10 (76.9%)	1 (33.3%)	11 (68.8%)	
Deceased	3 (23.1%)	2 (66.7%)	5 (31.3%)	

<sup>a</sup>Fisher's exact<sup>b</sup>Mann–Whitney U

Abbreviations: SEA = without anastomotic stenosis; CEA = with anastomotic stenosis; OR = odds ratio; CI = confidence interval.



**Figure 2.** Macroscopic and microscopic examination of a high-risk esophageal surgical specimen. A. Gross view of the resected esophagus showing loss of mucosal folds, ulcerations, and petechial hemorrhage. B. Close-up view highlighting mucosal erosion and the necrotic base of a large ulcer. C. Transverse histological section (H&E) showing mucosal ulceration, submucosal thickening, and disrupted muscularis mucosa. D. Corresponding Masson's trichrome stain showing extensive collagen deposition (blue) replacing muscular tissue (red). E–F. Longitudinal sections revealing architectural disruption and muscular fiber loss with dense connective tissue replacement.

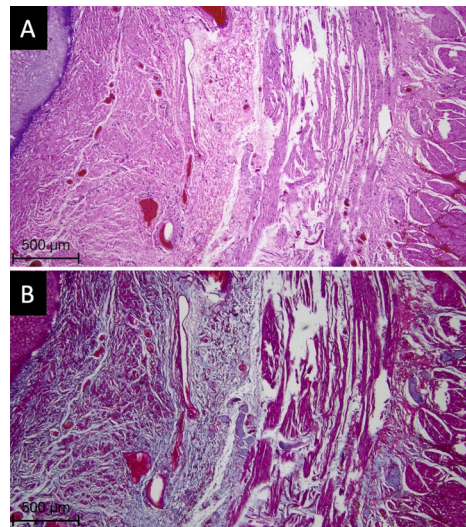
## Discussion

### *Histopathological Risk Patterns and Clinical Stenosis*

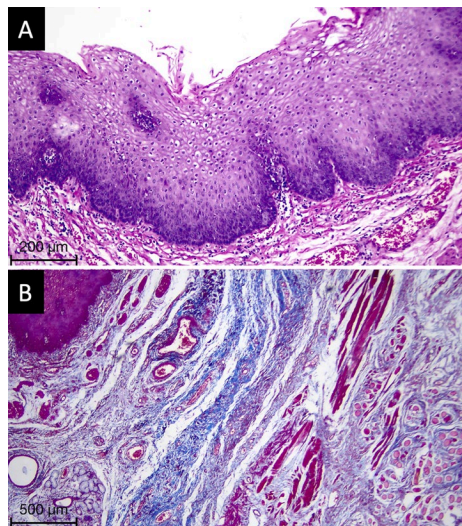
Across this exploratory cohort, higher composite histopathological scores—driven by collagen deposition and inflammatory infiltration—were associated with subsequent anastomotic stenosis. All stenosis cases mapped to the high-risk pattern ( $\geq 16$  points), supporting the clinical relevance of a layer-aware, multi-domain score for risk stratification in esophageal substitution.<sup>2,15,17</sup>

### *Inflammatory and Reparative Mechanisms of Fibrosis*

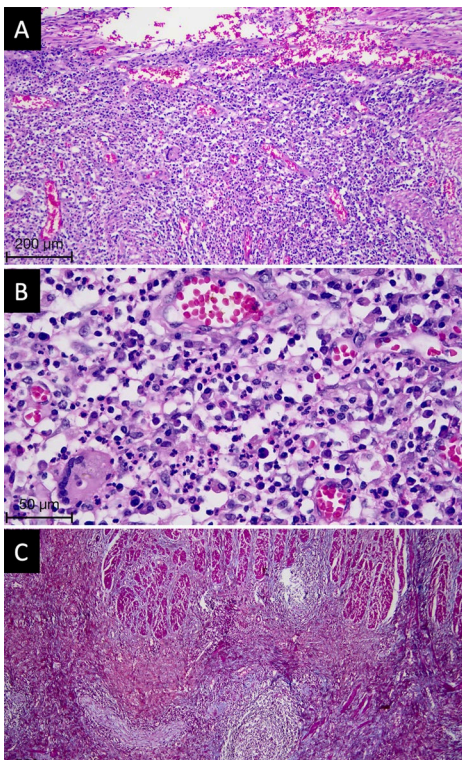
While prior research has largely focused on technical factors



**Figure 3.** Histological appearance of a low-risk esophageal sample with dominant fibrosis and minimal inflammation. A. Longitudinal section (H&E) showing increased submucosal thickness and mild disruption of the muscularis mucosa. B. Masson's trichrome stain demonstrating collagen replacement extending from the muscularis mucosa (1) through the submucosa (2) to the muscularis propria (3), in the absence of inflammatory infiltrate or granulation tissue. Total histopathological score: 4 (IN = 0, IL = 0, DC = 4, TG = 0).



**Figure 4.** Histological findings from a patient with chronic inflammation but limited fibrotic involvement. A. Interface between mucosa and submucosa showing severe chronic mononuclear inflammation (IL = 3), without granulation tissue. B. Masson's trichrome stain showing thinning of muscle fibers and focal collagen deposition. Total histopathological score: 8 (IN = 0, IL = 3, DC = 5, TG = 0).



**Figure 5.** Representative high-risk case with extensive inflammatory and fibrotic changes. A. Section showing dense neutrophilic (IN = 3) and mononuclear (IL = 3) infiltration, along with granulation tissue (TG = 3). B. Magnified view confirming inflammatory cell composition and submucosal involvement. C. Masson's trichrome stain revealing complete replacement of muscular architecture with thick collagen bundles (DC = 6). Total histopathological score: 15 (IN = 3, IL = 3, DC = 6, TG = 3).

such as tension, ischemia, and anastomotic leaks,<sup>18-20</sup> this study expands the understanding of underlying biological processes. Observed features (e.g., transition from acute neutrophilic to chronic lymphocytic inflammation, granulation tissue, and progressive collagen replacement) align with contemporary models of fibro-inflammatory remodeling in the esophagus and other tissues.<sup>10,14</sup> Experimental and translational data implicate macrophage-mediated pathways and matrix remodeling in stricture pathogenesis, offering mechanistic plausibility for the composite score's link with clinical stenosis.<sup>10,19,21</sup>

#### *Utility of a Composite Histopathological Score*

The composite score outperformed single-parameter readouts, indicating that integrating inflammation and repair across mucosal, submucosal, and muscular layers captures clinically meaningful biology. The visual spectrum in Figures 2–5 from minimal architectural change to extensive fibrotic replacement

corroborates this multidimensional approach and its face validity for surgical pathology workflows.

#### *Surgical Complications and Histological Correlation*

Leak-associated inflammation may accelerate fibrotic remodeling, creating a synergistic effect with pre-existing histological vulnerability.<sup>22,23</sup> No statistically significant association was demonstrated between anastomotic leak and stenosis in this sample; however, the point estimate suggested a possible relationship that merits evaluation in larger cohorts (OR 4.5; 95% CI 0.31–65.2). This cautious interpretation aligns with contemporary evidence that leak increases downstream stricture risk in broader populations.<sup>18,23</sup>

#### *Clinical Implications and Integration into Practice*

Incorporation of a standardized histopathological score into routine pathology reports could inform post-operative surveillance and early, tailored interventions in patients with high-risk tissue profiles. While definitive anti-fibrotic strategies in this setting remain to be defined, risk-guided follow-up is feasible now and may reduce procedure burden and morbidity.<sup>24</sup>

#### *Study Limitations and Future Directions*

This single-center, retrospective study and small sample size limit precision and preclude causal inference. Histology was restricted to native esophagus, without routine post-graft sampling. Future work should include multi-center validation, inter-observer agreement testing, and integration with molecular or imaging biomarkers, with linkage to long-term functional outcomes and quality of life.<sup>25-27</sup>

#### **Conclusion**

A composite, layer-aware histopathological score applied to native esophagus at substitution surgery stratified risk for anastomotic stenosis and showed concordance with clinical outcomes. Pending external validation, embedding this framework into surgical pathology may support targeted surveillance and earlier interventions to improve outcomes after esophageal reconstruction.

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