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Dynamic Changes in Inflammatory Cytokines and T-Lymphocyte Subsets after Endoscopic Submucosal Dissection for Early Gastrointestinal Cancer

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ABSTRACT

Background & Aims: This study aimed to characterize the dynamic changes in inflammation and T-lymphocyte subsets for early gastrointestinal cancer before and after endoscopic submucosal dissection (ESD) (pre-ESD; postoperative days 1, 7, and 30).

Methods: A total of 189 patients with early gastrointestinal cancer who underwent ESD and achieved en bloc resection were enrolled, including 53 cases of early esophageal cancer, 55 cases of early gastric cancer, and 81 cases of early colorectal cancer. Patients were categorized into a non-R0 en bloc resection group (n=32), a non-curative R0 resection group (n=62), and a curative resection group (n=95). Clinical characteristics, T-lymphocyte subsets, inflammatory markers, and postoperative complications were analyzed.

Results: ESD significantly ameliorated T-lymphocyte subsets and inflammatory cytokines, with the most pronounced improvement observed in the curative resection group. Pre- and post-ESD levels of these markers were significantly correlated with lesion size, tumor morphology, and depth of invasion. The non-R0 en bloc resection group had a markedly higher complication rate than the other groups, whereas the curative resection group showed the lowest rate. Improvements in immune and inflammatory indices after ESD did not differ significantly among early cancers of different sites. The postoperative complication incidence was not associated with tumor sites.

Conclusions: ESD markedly ameliorates the imbalance between T-lymphocyte subsets and inflammatory cytokine levels in early gastrointestinal cancer, with these indicators showing strong correlations with lesion size, tumor morphology, and depth of invasion. Curative resection demonstrates the greatest therapeutic benefit and the lowest postoperative complication rate.

Key words: endoscopic submucosal dissection – ESD – early gastrointestinal cancer – inflammatory factors – T-lymphocyte subsets – postoperative complications.

Abbreviations: CA19-9: carbohydrate antigen 19-9; CRP: C-reactive protein; ECC: early colorectal cancer; EEC: early esophageal cancer; EGC: early gastric cancer; ESD: endoscopic submucosal dissection; IL: interleukin; NEUT: neutrophil count; PLT: platelet count; POD: postoperative day; Tc: T cytotoxic; Te: T effector; Th: T helper; TNF-α: tumor necrosis factor-α; Treg: regulatory T cells; WBC: white blood cell count.

INTRODUCTION

Early gastrointestinal cancer refers to early-stage malignancies arising in the gastrointestinal tract (including the esophagus, stomach, and colorectum) in which the tumor is confined to the mucosal or submucosal layers without lymph node involvement or distant metastasis [1-3]. Clinically, early gastrointestinal cancer is classified into early esophageal cancer (EEC), early colorectal cancer (ECC), and early gastric cancer (EGC), based on the lesion's location [4]. At present, most upper gastrointestinal tumors are diagnosed at intermediate or advanced stages, resulting in a relatively low 5-year survival rate [5-7]. In contrast, early detection followed by endoscopic intervention can substantially improve the 5-year survival rate [8-10]. Therefore, early diagnosis and minimally invasive endoscopic treatment of gastrointestinal malignancies have become major focal points in contemporary digestive endoscopy.

Endoscopic submucosal dissection (ESD) is a complex resection technique designed for the en bloc excision of dysplastic and early-stage malignant gastrointestinal lesions

[11]. This minimally invasive approach effectively addresses lesions limited to the mucosa and submucosa, thus maintaining organ function and minimizing the necessity for more extensive surgical procedures [12]. However, ESD requires a high level of endoscopic expertise, and postoperative adverse events such as pain, esophageal stricture, gastrointestinal perforation, and bleeding may occur [13-15]. As an invasive intervention, ESD inevitably causes mucosal injury and triggers a systemic inflammatory response [16]. This response is characterized by inflammatory cell infiltration, neovascularization, and the presence of highly contractile myofibroblasts, which ultimately lead to scar formation and subsequent complications. For instance, esophageal stricture is a common complication after ESD for early esophageal cancer and can lead to varying degrees of dysphagia, thereby impairing patients' quality of life [17]. Therefore, identifying measurable biomarkers that reflect the severity of the post-ESD inflammatory state is essential for predicting complications and guiding therapeutic interventions.

Immune cells and cytokines serve as key regulators and participants in acute wound healing [18]. Inflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-α (TNF-α) are core indicators reflecting the host inflammatory state, and their dynamic changes mirror the intensity and duration of postoperative inflammation [19, 20]. T lymphocytes, crucial components of cellular immunity, contribute significantly to humoral immunity and sustain the body's immune function [21]. T-lymphocyte subsets included T helper (Th; also referred to as cluster of differentiation 4 $(CD4)^+$ T cells), T cytotoxic (Tc; also known as $CD8^+$ T cells), T effector (Te), and regulatory T (Treg) cells [22]. Studies have shown that IL-6 can inhibit Treg cell differentiation, leading to reduced Treg cell levels [23, 24]. During the subsequent reparative phase, however, Treg cells may be recruited to dampen excessive immune activation and facilitate tissue repair [25, 26]. IL-10 is a potent immunosuppressive cytokine that has been shown to suppress T-cell function and maintain an immunoregulatory state by downregulating T helper 1 (Th1)-type cytokines while upregulating Th2-type cytokines [27-29]. These findings highlight the reciprocal regulatory relationship between inflammatory cytokines and T-lymphocyte subsets during postoperative recovery [29]. To date, the dynamic postoperative changes in inflammatory cytokines and T-lymphocyte subsets following ESD have not been reported. The present study was proposed to investigate the dynamic changes of inflammatory markers and T-cell subsets before ESD and at 1, 7, and 30 days postoperatively in patients with early gastrointestinal cancers involving different anatomical sites (esophagus, stomach, and colorectum), providing a basis for optimizing ESD postoperative management strategies in clinical practice.

METHODS

This study was approved by the Academic Ethics Committee of Heji Hospital Affiliated to Changzhi Medical College and was conducted in accordance with the *Declaration of Helsinki*. As this was a retrospective analysis involving only de-identified data, the requirement for informed patient consent was waived by the Ethics Committee.

Sample size estimation for this study was performed in advance using G*Power 3.0.10 software (Heinrich-Heine-Universität Düsseldorf, Germany) [30] (Supplementary file, Fig. 1). A one-way analysis of variance (ANOVA) was selected as the tested method. The parameters were set as follows: power = 0.80, $\alpha = 0.05$, a medium estimated effect size, and number of groups = 3. Using the ANOVA of "F tests: fixed effects, omnibus, one-way" module, the minimum required sample size for the F test was calculated to be 159.

Early esophageal cancer refers to esophageal cancer in which the lesions are confined to the mucosal and submucosal layers, without lymph node metastasis. Indications for ESD: (a) absolute indications: (1) T1a esophageal squamous cell carcinoma confined to the epithelial layer (M1) or lamina propria (M2), with no clinical evidence of lymph node metastasis, (2) premalignant lesions; (b) relative indications: lesions infiltrating the muscularis mucosae (M3) or submucosal superficial layer (T1b-SM1, submucosal invasion depth < 200 μm) in the absence of clinical evidence of lymph node metastasis [31, 32].

Early gastric cancer is defined as gastric cancer where the lesions are confined to the gastric mucosa or submucosa, without lymph node metastasis. Indications for ESD: (a) absolute indications: (1) differentiated mucosal cancers without ulceration (cT1a), (2) differentiated mucosal cancers ≤ 3 cm with ulceration (cT1a), (3) high-grade intraepithelial neoplasia (HGIN); (b) relative indications: undifferentiated mucosal cancers ≤ 2 cm without ulceration (cT1a) [33, 34].

Early colorectal cancer is defined as cancer cells infiltrating the submucosal layer after penetrating the muscular layer of colorectal mucosa, but without involvement of the muscularis propria. Indications for ESD: (a) absolute indications: tumors confined to the mucosal layer (cT1a); (b) relative indications superficial infiltration of submucosa (mucosal layer infiltration depth ≤ 1000 μm, cT1b), highly/moderately differentiated, absence of vascular invasion, and no ulceration [35-37].

Inclusion criteria were: (1) aged ≥ 18 years with complete clinical data; (2) meeting the diagnostic criteria for early gastrointestinal cancer (EEC, EGC, or ECC); (3) undergoing ESD for the first time and achieving ESD en bloc resection; (4) fulfilling the indications for ESD and successfully completing the surgery; (5) complete clinical and follow-up information.

Exclusion criteria were: (1) concurrent with severe cardiac, pulmonary, renal, or coagulation dysfunction; (2) preoperative infectious shock; (3) history of prior ESD; (4) presence of other primary cancers; (5) incomplete clinical data; (6) diagnosed psychiatric disorders; (7) presence of other severe basic comorbidities; (8) postoperative use of corticosteroids for stricture prevention; (9) postoperative use of antibiotics.

This study retrospectively selected 206 patients who underwent ESD for early gastrointestinal cancer at Heji Hospital Affiliated to Changzhi Medical College between January 2022 and January 2025, and achieved ESD en bloc resection. Of these, 6 were excluded due to incomplete clinical data, and 11 were excluded based on inclusion and exclusion criteria.

Ultimately, 189 patients were enrolled in the study, including 53 with EEC, 55 with EGC, and 81 with ECC. According to the ESD resection type, patients were categorized

into three groups: non-R0 en bloc resection (n=32), non-curative R0 resection (n=62), and curative resection (n=95). Among them, 16.93% of cases (9 EEC, 10 EGC, and 13 ECC) underwent non-R0 en bloc resection; 32.80% (23 EEC, 13 EGC, and 26 ECC) underwent non-curative R0 resection; and 50.27% (21 EEC, 32 EGC, and 42 ECC) achieved curative resection.

Clinical data were collected for all patients, including sex, age, body mass index (BMI), smoking and drinking history, family history of esophageal, gastric, or colorectal cancer, main lesion size, lesion location, circumferential extent, tumor subtypes, infiltration depth, degree of differentiation, pathological grade, horizontal/vertical margin status (whether clear), presence of vascular invasion, and the incidence of postoperative complications (including bleeding, perforation, infection, esophageal stricture, gastric cavity deformity, and intestinal stenosis).

Fasting peripheral venous blood samples were obtained preoperatively and on postoperative day (POD) 1, 7, and 30. Laboratory indicators included carbohydrate antigen 19-9 (CA19-9), white blood cell count (WBC), platelet count (PLT), neutrophil count (NEUT), T-lymphocyte subsets (Treg cell, $CD3^+$, $CD4^+$ [Th1, Th2, Th17], $CD8^+$), and corresponding ratios ($CD4^+/CD8^+$, Th1/Th2, Th17/Treg, Th1/Th17), as well as inflammatory-related factors including CRP, IL-6, TNF-α, IL-1β, and IL-10.

ESD Resection

(1) En bloc resection by ESD: complete removal of the visible target lesion as a single specimen.

(2) Complete (R0) resection by ESD: en bloc resection and histological evaluation showed no tumor residue at the lateral and deep margins.

(3) Curative resection by ESD: an R0 resection accompanied by favorable histological features. Favorable histological criteria include: well to moderately differentiated degree, absence of lymphovascular invasion, and absence of deep infiltration or tumor budding. The invasion depth was defined based on anatomical site and cancer type. For esophageal and gastric adenocarcinoma, curative resection is defined as submucosal infiltration depth < 500 μm below the muscularis propria. For colorectal adenocarcinoma, curative resection is deemed as submucosal invasion depth < 1000 μm. In contrast, for esophageal squamous cell carcinoma, given its higher risk of lymph node metastasis, lesions invading the muscularis propria (m3) or infiltrating into the submucosa are not considered curatively resected [38-40].

Postoperative Management of ESD Treatment

(1) Diet: patients were kept fasting on POD 1. If no postoperative discomfort occurred, a full-liquid diet was initiated on POD 2, followed by a soft diet for the subsequent 3 days, and then gradually advanced to a regular diet.

(2) Acid suppression: intravenous proton pump inhibitors (PPIs) were administered to facilitate healing of iatrogenic ulcers. If no discomfort, treatment was transitioned to standard-dose oral PPIs after 2-3 days, with a recommended duration of 4-8 weeks.

(3) Complications: patients were monitored for signs of melena, hematemesis, and presence of subcutaneous emphysema in the head, neck, or chest. Vital signs were closely observed, and relevant laboratory or imaging examinations were performed when necessary. In cases of postoperative bleeding, perforation, or stricture, further therapeutic interventions were implemented based on the specific clinical condition.

Postoperative Complications of ESD

(1) Postoperative fever: an axillary temperature ≥ 37.3°C at any time during hospitalization after ESD, regardless of duration.

(2) Postoperative bleeding: hematemesis or melena occurring during hospitalization after ESD, instability of vital signs, or a 2 g/dL decrease in hemoglobin (Hb) compared with preoperative levels, as well as any bleeding event requiring endoscopic, interventional, or even surgical hemostasis [35, 41].

(3) Postoperative perforation: presence of clinical symptoms such as fever, abdominal pain, or peritonitis after ESD surgery; physical signs such as subcutaneous emphysema of the anterior chest or neck; elevated laboratory infection indicators; postoperative abdominal X-ray or computed tomography scan revealing intra-abdominal free air; or visible perforation identified under secondary endoscopy [42, 43].

Statistical Analysis

Data analyses and graphing were performed using SPSS statistical software (27.0; IBM Corp., Armonk, NY, USA) and MedCalc software (20.0; MedCalc Software Ltd., Ostend, Belgium). The Shapiro-Wilk test was used to assess the normality of data distribution. Measurement data with a normal distribution were expressed as mean ± standard deviation (SD). An independent sample *t* test was used for comparisons of these data between the two groups, while their comparisons among multiple groups were performed using one-way ANOVA, followed by Tukey's multiple comparisons test. Non-normally distributed measurement data were presented as quartiles, i.e., median (minimum, maximum). For these data, comparisons between two groups were performed using the Mann-Whitney test, and comparisons among multiple groups were performed using the Kruskal-Wallis test, followed by Dunn's multiple comparisons test. Count data were expressed as case numbers, and comparisons of binary variables between groups were performed using the Chi-square test/Chi-Square Goodness-of-Fit Test. All p-values were two-sided, and statistical significance was defined as $p < 0.05$.

RESULTS

Comparative analyses of T-lymphocyte subsets (Treg cell, $CD3^+$, $CD4^+$ [Th1, Th2, Th17], $CD8^+$, $CD4^+/CD8^+$, Th1/Th2, Th17/Treg cell, and Th1/Th17 ratios) and inflammatory markers (CRP, IL-6, TNF-α, and IL-10) were performed before ESD and at 1, 7, and 30 d post ESD (Table I). The results showed that, compared with preoperative levels, Treg cells decreased on POD 1, increased on POD 7, and declined again by POD 30. Meanwhile, compared with pre-operation, Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, and Th1/Th17 levels demonstrated a time-dependent pattern of initial reduction followed by subsequent elevation on POD 1, 7, and

30. Conversely, Th17, $CD8^+$, Th2, CRP, and IL-10 levels exhibited a trend of first increase and subsequent decline with time on POD 1, 7, and 30 compared with pre-operation (all $p< 0.05$). Compared with POD 1, immune function and inflammatory markers, including Th2, Th17, CRP, IL-6, TNF-α, and IL-10, were gradually decreased on POD 7 and 30, whereas Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, Th17/Treg cell, and Th1/Th17 increased in a time-dependent manner (all $p< 0.05$).

Table I. Comparison of preoperative and postoperative T-lymphocyte subsets and inflammatory factors in patients with early gastrointestinal cancer

	Preoperative 1 d	POD 1	POD 7	POD 30
Treg (%$CD4^+$T)	10.08 (7.92, 12.16)	7.96 (6.03, 9.98)^{aa}	11.37 (8.49, 14.56)^{aabb}	7.97 (5.90, 10.32)^{aacc}
Th1 (%$CD4^+$T)	15.12 (11.19, 18.97)	12.96 (8.70, 17.00)^{aa}	17.17 (12.55, 22.69)^{aabb}	21.96 (14.42, 28.53)^{aabbcc}
Th2 (%$CD4^+$T)	13.29 (7.18, 17.32)	14.88 (9.82, 20.05)^{aa}	13.49 (9.63, 16.08)^{abb}	10.83 (6.23, 14.13)^{aabbcc}
Th17 (%$CD4^+$T)	5.23 (2.91, 7.40)	7.66 (4.91, 10.20)^{aa}	5.21 (3.29, 8.04)^{bb}	4.15 (1.58, 6.16)^{aabbc}
$CD4^+$ (%$CD3^+$T)	34.72 (25.54, 45.44)	30.14 (22.27, 41.49)^{aa}	33.06 (23.75, 45.12)^{aabb}	40.39 (28.43, 50.20)^{aabbcc}
$CD8^+$ (%$CD3^+$T)	30.53 (24.96, 35.36)	32.45 (31.01, 37.30)^{aa}	35.00 (32.23, 40.89)^{aabb}	29.02 (24.54, 36.09)^{bbcc}
$CD4^+/CD8^+$	1.16 (0.78, 1.80)	0.83 (0.55, 1.20)^{aa}	0.94 (0.66, 1.30)^{abb}	1.40 (0.99, 1.71)^{aacc}
Th1/Th2	1.16 (0.72, 2.55)	0.88 (0.47, 1.50)^{aa}	1.26 (0.82, 2.10)^{aabb}	2.01 (1.16, 4.23)^{aabbcc}
Th17/Treg	0.49 (0.26, 0.85)	0.94 (0.50, 1.58)^{aa}	0.46 (0.27, 0.84)^{aabb}	0.51 (0.19, 0.91)^{bbc}
Th1/Th17	2.85 (1.81, 6.37)	1.73 (0.87, 3.01)^{aa}	3.36 (1.81, 6.18)^{aabb}	5.30 (2.76, 17.08)^{aabbcc}
CRP (mg/L)	7.22 (1.59, 12.26)	55.29 (35.15, 82.74)^{aa}	26.09 (7.33, 40.73)^{aabb}	4.29 (1.29, 15.26)^{aabbcc}
IL-6 (pg/mL)	4.04 (0.93, 7.04)	134.45 (53.32, 201.32)^{aa}	26.89 (10.23, 73.84)^{aabb}	3.67 (0.76, 7.13)^{bbcc}
TNF-α (pg/mL)	4.36 (1.00, 7.60)	75.74 (29.86, 116.04)^{aa}	21.24 (8.08, 58.33)^{aabb}	3.96 (0.82, 7.70)^{bbcc}
IL-10 (pg/mL)	13.03 (8.71, 15.62)	26.11 (15.43, 35.79)^{aa}	17.76 (9.06, 27.59)^{aabb}	10.08 (6.79, 18.58)^{aabbcc}

POD: postoperative day; Treg: regulatory T cells; IL-10: interleukin-10; Th1: T helper 1 cells; Th2: T helper 2 cells; Th17: T helper 17 cells; CD3: cluster of differentiation 3; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha. Normal distribution test was performed using the Kolmogorov-Smirnov test. Non-normally distributed measurement data were presented as quartile, i.e., median (minimum, maximum). For comparisons among multiple groups, the Kruskal-Wallis H test was used, followed by Dunn's multiple comparisons test. Compared to preoperative day 1: ^{a}: $p<0.05$, ^{aa}: $p<0.01$; compared to POD 1; ^{b}: $p<0.05$, ^{bb}: $p<0.01$; compared to POD 7, ^{c}: $p<0.05$, ^{cc}: $p<0.01$.

To investigate the correlations of T lymphocyte subsets and inflammatory factors with imaging techniques (tumor morphology and depth of invasion) or EUS indicators (primary lesion size) in patients with early gastrointestinal cancer before and after ESD, we performed subgroup analyses based on primary lesion size (median: 3.04 cm), tumor morphology, and depth of invasion. The major results are summarized in Table II. Patients with a primary lesion size > 3.04 cm showed significantly higher levels of Treg cells (preoperatively and on POD 1 and 7), CRP and TNF-α (preoperatively and on POD 1, 7, and 30), and IL-6 (on POD 1 and 7) than those with lesions ≤ 3.04 cm; conversely, the levels of Th1 cells and the Th1/Th2 ratio (preoperatively), $CD4^+$ cells and $CD4^+/CD8^+$ ratio (preoperatively and on POD 1 and 7), as well as the Th17/Treg cell ratio (preoperatively and on POD 1), were significantly lower (all $P < 0.05$) in the patients with a primary lesion size > 3.04 cm versus those with a primary lesion size ≤ 3.04 cm. These findings suggest that larger tumor volume is associated with more pronounced preoperative and postoperative immunosuppression and an enhanced inflammatory response.

Compared with patients with protruding lesions, those with flat or depressed lesions exhibited higher levels of Treg cells (POD 7 and 30), CRP (preoperatively and on POD 1, 7, and 30), TNF-α (POD 1, 7, and 30), and IL-6 (preoperatively and on POD 1 and 7). Conversely, Th1 cells (preoperatively and on POD 1 and 7), $CD4^+$ cells (preoperatively and on POD 1, 7, and 30), the $CD4^+/CD8^+$ ratio (preoperatively and on POD 7 and 30), the Th1/Th2 ratio (preoperatively), and the Th1/Th17 ratio (preoperatively and on POD 1) were all significantly reduced (all $P < 0.05$). These findings show that flat and depressed tumors may induce stronger inflammatory responses and more marked immunosuppression, with relatively slower postoperative immune recovery.

Furthermore, compared to patients with the mucosal layer invasion, those with submucosal invasion showed increased levels of Treg and Th17 cells (preoperatively and on POD 1, 7, and 30), Th2 cells (preoperatively and on POD 1 and 7), the Th17/Treg cell ratio (POD 30), CRP (preoperatively and on POD 1 and 30), TNF-α (preoperatively and on POD 1, 7, and 30), and IL-6 (preoperatively). In contrast, Th1 cells and the Th1/Th2 ratio (preoperatively and on POD 1), as well as the Th1/Th17 ratio (preoperatively and on POD 1 and 30), were significantly decreased (all $P < 0.05$). This indicates that deeper tumor invasion is associated with more pronounced immunosuppression and aggravated inflammatory response.

These findings collectively indicate that in patients with early gastrointestinal cancer, T lymphocyte subsets and inflammatory factors before and after ESD are closely correlated with lesion size, tumor morphology, and depth of invasion.

Table II. Correlation analysis of T-lymphocyte subsets and inflammatory markers with imaging techniques or endoscopic ultrasound (EUS) indicators before and after ESD in early gastrointestinal cancer patients

		Lesion size (median: 3.04 cm)		Tumor morphology		Depth of invasion	
		≤ 3.04 (n = 95)	> 3.04 (n = 94)	Elevated (n = 68)	Flat and depressed (n = 121)	Mucosal layer (n = 26)	Submucosal layer (n = 163)
Treg (%CD4⁺T)	Pre-operation	9.75 (8.25, 12.16)	10.35 (7.92, 11.98)^{aa}	9.99 (7.92, 11.94)	10.08 (8.25, 12.16)	9.35 (8.49, 11.81)	10.22 (7.92, 12.16)^{cc}
	POD 1	7.61 (6.03, 9.96)	8.17 (6.14, 9.98)^{aa}	7.95 (6.13, 9.85)	7.98 (6.03, 9.98)	7.18 (6.03, 9.58)	8.11 (6.13, 9.98)^{cc}
	POD 7	11.16 ± 1.25	11.59 ± 1.29^{a}	11.02 (8.49, 13.64)	11.53 (9.29, 14.56)^{b}	10.83 ± 1.43	11.46 ± 1.24^{c}
	POD 30	7.92 (5.90, 10.32)	8.08 (6.31, 10.27)	7.90 (5.90, 9.49)	8.07 (6.36, 10.32)^{b}	7.51 (5.90, 9.29)	8.05 (6.36, 10.32)^{c}
Th1 (%CD4⁺T)	Pre-operation	15.33 (11.19, 18.97)	14.64 (11.23, 18.58)^{a}	15.52 (11.81, 18.97)	14.82 (11.19, 18.79)^{bb}	16.75 (13.45, 18.66)	14.82 (11.19, 18.97)^{cc}
	POD 1	13.31 (8.99, 16.91)	12.85 (8.70, 17.00)	13.79 (9.06, 17.00)	12.49 (8.70, 16.91)^{b}	15.06 (9.13, 16.91)	12.96 (8.70, 17.00)^{c}
	POD 7	17.17 (12.87, 22.69)	17.27 (12.55, 21.88)	17.90 ± 2.40	17.10 ± 2.24^{b}	17.27 ± 2.68	17.41 ± 2.27
	POD 30	21.38 (15.31, 28.36)	22.18 (14.42, 28.53)	22.48 ± 3.17	21.77 ± 3.21	21.55 (15.31, 28.53)	22.00 (14.42, 28.36)
Th2 (%CD4⁺T)	Pre-operation	12.85 (7.18, 17.29)	13.87 (7.30, 17.32)	13.26 (7.30, 17.07)	13.42 (7.18, 17.32)	10.13 (7.20, 16.96)	13.58 (7.18, 17.32)^{cc}
	POD 1	14.86 (10.98, 20.05)	14.99 (9.82, 19.63)	14.63 (11.33, 20.05)	14.99 (9.82, 19.93)	13.64 (9.82, 18.39)	15.00 (11.31, 20.05)^{c}
	POD 7	13.45 (9.63, 16.01)	13.63 (11.23, 16.08)	13.82 (10.44, 16.01)	13.34 (9.63, 16.08)	12.74 (9.63, 15.7)	13.54 (10.33, 16.08)^{c}
	POD 30	11.19 (6.23, 13.65)	10.69 (6.24, 14.13)	10.54 (6.23, 14.13)	11.05 (6.24, 13.65)	11.19 (6.32, 13.32)	10.75 (6.23, 14.13)
Th17 (%CD4⁺T)	Pre-operation	5.39 (2.91, 7.40)	5.02 (2.93, 7.37)	5.26 (2.92, 7.40)	5.23 (2.91, 7.37)	4.44 (2.91, 6.59)	5.39 (2.93, 7.40)^{cc}
	POD 1	7.60 (4.92, 10.11)	7.68 (4.91, 10.20)	7.37 (4.91, 10.15)	7.75 (4.92, 10.20)	6.27 (4.91, 8.81)	7.79 (4.92, 10.20)^{cc}
	POD 7	5.22 (3.33, 7.81)	5.02 (3.29, 8.04)	5.25 (3.29, 7.68)	5.15 (3.33, 8.04)	4.5 (3.29, 6.96)	5.26 (3.33, 8.04)^{c}
	POD 30	4.33 (1.66, 6.16)	3.94 (1.58, 6.03)	4.26 (1.64, 6.16)	4.15 (1.58, 6.14)	3.58 (1.58, 5.29)	4.37 (1.66, 6.16)^{cc}
CD4⁺ (%CD3⁺T)	Pre-operation	36.34 (25.95, 45.44)	33.46 (25.54, 43.41)^{aa}	35.82 (26.85, 45.44)	34.34 (25.54, 44.88)^{bb}	33.80 (27.29, 44.88)	34.73 (25.54, 45.44)
	POD 1	30.94 (22.81, 41.49	30.00 (22.27, 39.04)^{a}	31.46 (22.81, 39.25)	29.65 (22.27, 41.49)^{b}	29.12 ± 4.18	30.71 ± 4.40
	POD 7	34.18 (24.18, 45.12)	32.24 (23.75, 42.15)^{aa}	34.34 (25.15, 42.15)	32.10 (23.75, 45.12)^{bb}	30.88 (23.75, 40.89)	33.26 (23.88, 45.12)
	POD 30	39.32 (29.67, 49.98)	41.82 (28.43, 50.20)	40.88 (30.43, 49.99)	39.95 (28.43, 50.20)^{b}	37.63 (29.37, 45.01)	40.78 (28.43, 50.20)^{c}
CD8⁺ (%CD3⁺T)	Pre-operation	30.90 (25.02, 35.36)	30.23 (24.96, 35.34)	30.38 (25.47, 35.36)	30.58 (24.96, 35.34)	30.63 (25.63, 34.95)	30.53 (24.96, 35.36)
	POD 1	36.13 (31.22, 40.25)	36.62 (31.03, 40.89)	36.53 (31.01, 40.89)	36.37 (31.19, 40.87)	36.12 (31.22, 40.48)	36.51 (31.01, 40.89)
	POD 7	34.92 ± 1.17	34.96 ± 1.10	35.07 (32.23, 37.11)	34.95 (32.42, 37.30)	34.83 (32.80, 36.94)	35.04 (32.23, 37.30)
	POD 30	29.10 ± 2.55	29.34 ± 2.83	28.56 (24.55, 34.53)	29.07 (24.54, 36.09)	29.29 (24.63, 35.39)	28.88 (24.54, 36.09)
CD4⁺/CD8⁺	Pre-operation	1.20 ± 0.18	1.13 ± 0.19a	1.21 ± 0.17	1.14 ± 0.18bb	1.15 ± 0.18	1.17 ± 0.18
	POD 1	0.87 ± 0.13	0.82 ± 0.14aa	0.87 ± 0.14	0.83 ± 0.13	0.82 ± 0.13	0.85 ± 0.14
	POD 7	0.98 (0.72, 1.25)	0.91 (0.67, 1.22)^{aa}	0.99 (0.73, 1.22)	0.92 (0.67, 1.25)^{bb}	0.87 (0.67, 1.12)	0.96 (0.67, 1.25)
	POD 30	1.38 (0.89, 1.82)	1.42 (0.99, 1.95)	1.43 (1.03, 1.95)	1.39 (0.89, 1.71)^{b}	1.35 (1.01, 1.64)	1.42 (0.89, 1.95)

Table II (continued)

Th1/Th2	Pre-operation	1.18 (0.75, 2.55)	1.11 (0.72, 2.29)[a]	1.21 (0.82, 2.29)	1.13 (0.72, 2.55)[b]	1.48 (0.90, 2.29)	1.14 (0.72, 2.55)[cc]
	POD 1	0.85 (0.50, 1.54)	0.87 (0.53, 1.58)	0.89 (0.51, 1.50)	0.83 (0.50, 1.58)	0.99 (0.60, 1.58)	0.84 (0.50, 1.50)[cc]
	POD 7	1.27 (0.88, 2.07)	1.24 (0.82, 1.83)	1.32 (0.82, 2.06)	1.23 (0.88, 2.07)	1.33 (0.97, 2.07)	1.24 (0.82, 2.06)
	POD 30	1.92 (1.16, 4.23)	2.07 (1.41, 4.00)[a]	2.13 (1.26, 4.23)	1.96 (1.16, 4.00)	1.91 (1.22, 3.44)	2.04 (1.16, 4.23)
Th17/Treg	Pre-operation	0.53 (0.29, 0.85)	0.48 (0.26, 0.78)[a]	0.49 (0.27, 0.79)	0.50 (0.26, 0.85)	0.45 (0.31, 0.78)	0.50 (0.26, 0.85)
	POD 1	0.97 (0.52, 1.58)	0.92 (0.56, 1.43)[a]	0.90 (0.56, 1.43)	0.94 (0.52, 1.58)	0.89 (0.64, 1.37)	0.94 (0.52, 1.58)
	POD 7	0.48 (0.28, 0.70)	0.45 (0.28, 0.80)	0.48 (0.28, 0.80)	0.46 (0.28, 0.71)	0.43 (0.29, 0.70)	0.47 (0.28, 0.80)
	POD 30	0.53 ± 0.16	0.49 ± 0.15	0.53 ± 0.17	0.50 ± 0.16	0.42 ± 0.17	0.52 ± 0.16[cc]
Th1/Th17	Pre-operation	2.91 (1.81, 6.37)	2.84 (1.96, 5.67)	3.07 (1.87, 6.37)	2.78 (1.81, 5.65)[b]	3.83 (2.05, 6.41)	2.8 (1.701, 5.18)[cc]
	POD 1	1.70 (1.04, 2.97)	1.74 (0.93, 3.01)	1.82 (1.03, 3.01)	1.62 (0.93, 2.91)[bb]	2.22 (1.21, 2.91)	1.68 (0.93, 3.01)[cc]
	POD 7	3.36 (1.82, 5.91)	3.38 (1.81, 6.10)	3.42 (1.81, 6.10)	3.33 (1.82, 6.08)	3.49 (2.11, 6.10)	3.36 (1.81, 6.08)
	POD 30	5.25 (2.76, 17.08)	5.66 (3.00, 16.80)	5.26 (2.94, 12.90)	5.37 (2.76, 17.08)	7.24 (2.89, 16.80)	5.10 (2.76, 17.08)[cc]
CRP (mg/L)	Pre-operation	6.76 (1.59, 10.00)	7.67 (2.94, 12.26)[a]	6.31 (1.59, 10.90)	7.58 (2.92, 12.26)[bb]	5.77 (1.59, 9.76)	7.45 (4.03, 12.26)[c]
	POD 1	54.00 (35.15, 7.88)	57.85 (36.72, 82.74)[a]	52.72 (31.15, 73.96)	57.35 (37.16, 82.74)[bb]	53.71 ± 10.82	55.50 ± 10.40
	POD 7	24.55 (7.33, 36.34)	28.07 (7.47, 40.73)[a]	24.15 (7.33, 34.50)	27.84 (7.84, 40.73)[b]	21.62 (7.33, 32.61)	26.95 (7.84, 40.73)[c]
	POD 30	4.11 (1.29, 7.64)	4.51 (1.59, 15.26)[a]	3.63 (1.16, 6.75)	4.53 (1.29, 15.26)[bb]	3.31 (1.29, 6.83)	4.39 (1.39, 15.26)[cc]
IL-6 (pg/mL)	Pre-operation	4.11 (0.93, 7.04)	3.93 (1.51, 6.81)	3.43 (1.49, 6.81)	4.27 (0.93, 7.04)[bb]	3.83 (1.51, 6.24)	4.11 (0.93, 7.04)
	POD 1	120.50 (53.32, 193.80)	141.10 (64.57, 201.30)[aa]	120.70 (53.32, 200.90)	139.20 (64.23, 201.30)[b]	112.30 (54.80, 181.60)	136.70 (53.32, 201.30)[c]
	POD 7	25.95 (10.23, 55.26)	29.75 (10.73, 73.84)[a]	25.45 (10.73, 56.70)	27.62 (10.23, 73.84)[b]	25.85 (10.23, 41.65)	27.30 (10.23, 73.84)
	POD 30	3.15 (0.76, 7.13)	4.17 (0.79, 7.06)	3.14 (0.79, 7.13)	3.93 (0.76, 7.06)	2.86 (0.79, 7.06)	4.01 (0.76, 7.13)
TNF-α (pg/mL)	Pre-operation	3.84 (1.00, 7.15)	4.72 (2.45, 7.60)[aa]	3.96 (1.63, 7.60)	4.48 (1.00, 7.35)	3.06 (1.61, 5.58)	4.63 (1.00, 7.60)[cc]
	POD 1	69.11 (29.86, 108.60)	80.29 (37.19, 116.00)[aa]	68.39 (29.86, 110.20)	79.59 (36.16, 116.00)[bb]	55.32 (36.59, 110.20)	78.16 (29.86, 116.00)[cc]
	POD 7	20.23 (8.08, 43.66)	23.58 (8.08, 58.33)[aa]	19.68 (8.08, 44.41)	23.24 (8.08, 58.33)[bb]	17.99 (8.08, 32.49)	21.65 (8.48, 58.33)[cc]
	POD 30	3.29 (0.82, 7.70)	0.54 (0.85, 7.62)[a]	3.30 (0.85, 7.25)	4.35 (0.82, 7.70)[b]	2.96 (0.82, 7.62)	4.40 (0.90, 7.70)[cc]
IL-10 (pg/mL)	Pre-operation	13.11 (8.86, 15.62)	12.89 (8.71, 15.51)	12.81 (8.81, 15.54)	13.14 (8.71, 15.62)	12.44 (9.29, 15.54)	13.14 (8.71, 15.62)
	POD 1	26.06 (15.43, 35.79)	26.21 (16.18, 34.76)	25.50 (16.27, 34.23)	26.16 (15.43, 35.79)	25.73 (16.18, 35.79)	26.11 (15.43, 34.76)
	POD 7	17.56 (9.06, 27.58)	18.08 (11.39, 27.59)	18.15 ± 3.64	17.94 ± 3.77	17.83 ± 3.96	18.04 ± 3.69
	POD 30	9.93 (6.85, 15.14)	10.33 (6.79, 18.58)	9.76 (6.79, 15.14)	10.22 (6.85, 18.58)	10.40 (6.88, 15.24)	10.07 (6.79, 18.58)

EUS: endoscopic ultrasound; ESD: endoscopic submucosal dissection; For the rest of abbreviations see Table I. Normality test was performed using the Kolmogorov-Smirnov test. Non-normally distributed measurement data were presented as the median (minimum, maximum) and were compared between two groups using the Mann-Whitney test. Normally distributed measurement data were expressed as mean ± SD and were compared using the independent-samples t-test. Compared with ≤ 3.04: [a]: $p<0.05$ and [aa]: $p<0.01$; compared with the protruding lesions: [b]: $p<0.05$ and [bb]: $p<0.01$; compared with the mucosal layer invasion: [c] $p< 0.05$ and [cc] $p<0.01$.

Patients were stratified into three groups based on the type of ESD resection: non-R0 en bloc resection (n=32), non-curative R0 resection (n=62), and curative resection (n=95). T-lymphocyte subsets and inflammatory markers among the three groups were compared preoperatively and on POD 1, 7, and 30 (Table III).

Table III. Comparisons of preoperative and postoperative T-lymphocyte subsets and inflammatory factors in patients with different types of ESD resection

		Non-R0 en bloc resection (n = 32)	Non-curative R0 resection (n = 62)	Curative resection (n = 95)
Treg (%CD4$^+$T)	Pre-operation	10.03 (8.25, 11.98)	9.94 (8.27, 11.95)	10.10 (7.92, 12.16)
	POD 1	9.08 (6.03, 9.96)^{aa}	7.52 (6.13, 9.83)^{ddaa}	7.92 (6.16, 9.98)^{ddaa}
	POD 7	12.57 (9.19, 14.50)^{aabb}	11.46 (8.49, 13.47)^{aabb}	11.11 (9.27, 14.56)^{dabb}
	POD 30	8.48 (5.90, 10.27)^{aabbcc}	8.29 (6.48, 10.32)^{aabbcc}	7.55 (6.31, 9.55)^{ddaacc}
Th1 (%CD4$^+$T)	Pre-operation	14.68 (11.43, 17.01)	15.30 (11.19, 18.97)	15.15 (11.37, 18.79)
	POD 1	12.63 (8.99, 16.69)^{aa}	12.27 (9.38, 16.96)^{aa}	13.74 (8.70, 17.00)^{aa}
	POD 7	15.97 (12.87, 18.96)^{aabb}	16.94 (12.55, 20.67)^{bb}	18.11 (14.47, 22.69)^{ddeeaabb}
	POD 30	20.76 (14.42, 27.36)^{aabbcc}	21.41 (17.14, 26.99)^{aabbcc}	22.89 (17.68, 28.53)^{ddeaabbcc}
Th2 (%CD4$^+$T)	Pre-operation	13.45 (7.20, 16.96)	13.73 (7.77, 17.29)	12.96 (7.18, 17.32)
	POD 1	15.00 (10.39, 18.56)^{aa}	14.77 (9.82, 20.05)^{aa}	14.87 (10.98, 19.30)^{aa}
	POD 7	13.56 (11.25, 16.08)^{aab}	13.72 (11.74, 16.01)^{bb}	13.31 (9.63, 16.07)^{aabb}
	POD 30	11.12 (8.93, 14.13)^{aabbcc}	10.92 (6.88, 13.59)^{aabbcc}	10.60 (6.23, 13.91)^{daabbcc}
Th17 (%CD4$^+$T)	Pre-operation	5.40 (2.93, 6.81)	4.95 (2.92, 7.40)	5.30 (2.91, 7.40)
	POD 1	7.90 (5.62, 10.05)^{aa}	7.52 (5.08, 10.00)^{aa}	7.60 (4.91, 10.20)^{aa}
	POD 7	5.31 (3.35, 8.04)^{b}	5.06 (3.33, 7.68)^{bb}	5.21 (3.29, 7.62)^{abb}
	POD 30	4.87 (1.59, 6.02)^{aabbcc}	3.99 (1.58, 6.14)^{aabbcc}	3.94 (1.64, 6.16)^{aabbcc}
CD4$^+$ (%CD3$^+$T)	Pre-operation	33.54 (25.84, 43.33)	34.34 (25.54, 43.41)	35.82 (26.32, 45.44)
	Postoperative 1d	29.59 ± 3.68^{aa}	30.84 ± 5.01^{aa}	30.56 ± 4.19^{aa}
	Postoperative 7d	30.80 (23.88, 41.23)^{aabb}	33.35 (23.94, 45.12)^{bb}	33.32 (23.75, 42.14)^{abb}
	Postoperative 30d	38.68 (28.66, 49.67)^{aabbcc}	41.37 (28.43, 49.06)^{aabbcc}	40.39 (29.67, 50.20)^{aabbcc}
CD8$^+$ (%CD3$^+$T)	Pre-operation	30.05 (24.96, 35.36)	30.26 (25.02, 35.34)	30.74 (25.63, 35.33)
	POD 1	36.44 (31.19, 40.78)^{aa}	36.12 (31.01, 40.75)^{aa}	36.52 (31.03, 40.89)^{aa}
	POD 7	34.80 (32.42, 36.62)^{aabb}	35.37 (32.23, 37.30)^{aa}	34.92 (32.33, 37.11)^{aabb}
	POD 30	28.92 (24.85, 34.86)^{aabbcc}	28.79 (24.69, 35.39)^{bbcc}	29.13 (24.54, 36.09)^{bbcc}
CD4$^+$/CD8$^+$	Pre-operation	1.14 ± 0.16	1.15 ± 0.18	1.18 ± 0.19
	POD 1	0.83 ± 0.12^{aa}	0.86 ± 0.16^{aa}	0.85 ± 0.13^{aa}
	POD 7	0.89 (0.67, 1.19)^{aab}	0.96 (0.68, 1.25)^{aabb}	0.96(0.67, 1.22)^{bbaa}
	POD 30	1.39 (0.99, 1.70)^{aabbcc}	1.41 (0.91, 1.82)^{aabcc}	1.42 (0.89, 1.95)^{aabcc}
Th1/Th2	Pre-operation	1.08 (0.79, 2.29)	1.15 (0.73, 2.18)	1.18 (0.72, 2.55)
	POD 1	0.83 (0.53, 1.58)^{aa}	0.85 (0.50, 1.58)^{aa}	0.88 (0.53, 1.54)^{aa}
	POD 7	1.22 (0.82, 1.52)^{abb}	1.23 (0.88, 1.72)^{bb}	1.32 (0.97, 2.07)^{ddeeaabb}
	POD 30	1.75 (1.16, 2.64)^{aabbcc}	1.95 (1.33, 3.39)^{aabbcc}	2.16 (1.41, 4.23)^{ddeaabbcc}
Th17/Treg	Pre-operation	0.49 (0.26, 0.78)	0.48 (0.29, 0.81)	0.51 (0.26, 0.85)
	POD 1	0.89 (0.63, 1.37)^{aa}	0.96 (0.56, 1.44)^{aa}	0.94 (0.52, 1.58)^{aa}
	POD 7	0.46 ± 0.12^{abb}	0.47 ± 0.10^{aabb}	0.48 ± 0.11^{aabb}
	POD 30	0.57 (0.18, 0.90)^{aabbc}	0.50 (0.19, 0.86)^{bbc}	0.50 (0.22, 0.83)^{bbc}
Th1/Th17	Pre-operation	2.59 (1.97, 5.48)	2.92 (1.83, 6.37)	2.89 (1.70, 6.41)
	POD 1	1.58 (1.13, 2.81)^{aa}	1.67 (0.99, 2.97)^{aa}	1.78 (0.93, 3.01)^{aa}
	POD 7	3.13 (1.82, 4.85)^{aabb}	3.36 (1.81, 5.16)^{aabb}	3.41 (2.03, 6.10)^{aabb}
	POD 30	4.49 (2.76, 13.84)^{aabbcc}	5.30 (2.93, 16.80)^{daabbcc}	5.75 (3.31, 17.08)^{ddaabbcc}
CRP (mg/L)	Pre-operation	7.90 (4.29, 9.97)	7.25 (1.59, 12.26)	6.65 (2.92, 10.91)
	POD 1	52.41 (36.21, 79.39)^{aa}	57.85 (35.15, 73.94)^{aa}	54.91 (36.72, 82.74)^{aa}
	POD 7	27.14 (7.33, 40.73)^{aabb}	25.02 (13.89, 35.94)^{aabb}	26.95 (7.47, 40.08)^{aabb}
	POD 30	3.95 (1.43, 15.26)^{aabbcc}	4.37 (1.46, 7.67)^{aabbcc}	4.21 (1.29, 11.13)^{aabbcc}

Table III (continued)

IL-6 (pg/mL)	Pre-operation	3.95 (1.74, 6.15)	4.06 (0.93, 6.68)	4.27 (1.49, 7.04)
	POD 1	138.90 (65.81, 200.10)^{aa}	126.00 (54.80, 200.90)^{aa}	135.70 (53.32, 201.30)^{aa}
	POD 7	30.50 (11.84, 55.26)^{aabb}	27.25 (10.23, 73.84)^{aabb}	26.00 (10.23, 59.93)^{aabb}
	POD 30	4.21 (1.48, 6.94)^{aabbcc}	3.22 (0.79, 6.81)^{aabbcc}	3.67 (0.76, 7.13)^{aabbcc}
TNF-α (pg/mL)	Pre-operation	4.23 (2.45, 6.64)	4.17 (1.00, 7.15)	4.68 (1.61, 7.60)
	POD 1	76.86 (31.78, 116.00)^{aa}	73.37 (37.19, 110.20)^{aa}	76.54 (29.86, 112.70)^{aa}
	POD 7	23.02 (8.48, 42.19)^{aabb}	20.82 (8.08, 58.33)^{aabb}	21.32 (8.08, 47.34)^{aabb}
	POD 30	4.56 (1.60, 7.50)^{aabbcc}	4.55 (0.85, 7.70)^{aabbcc}	3.27 (0.82, 7.62)^{aabbcc}
IL-10 (pg/mL)	Pre-operation	12.93 (8.86, 15.54)	13.18 (9.11, 15.62)	12.79 (8.71, 15.60)
	POD 1	26.02 (16.26, 35.79)^{aa}	26.09 (15.43, 34.31)^{aa}	26.16 (16.18, 34.76)^{aa}
	POD 7	20.03 (14.17, 27.59)^{aabb}	17.76 (12.88, 23.93)^{aabb}	16.85 (9.06, 26.50)^{ddaabb}
	POD 30	12.37 (9.93, 18.58)^{bbcc}	9.95 (7.95, 14.94)^{ddaabbcc}	9.38 (6.79, 14.81)^{ddaabbcc}

For abbreviations see Table I and II. Normal distribution test was performed using the Kolmogorov-Smirnov test. Measurement data with normal distribution were expressed as mean ± SD, and one-way ANOVA was used for comparison between groups, followed by Tukey's multiple comparisons test. Non-normally distributed measurement data were presented as the median (minimum, maximum), and comparisons among groups were performed using the Kruskal-Wallis test, followed by Dunn's multiple comparisons test for post hoc analysis. Compared to preoperative day 1: ^{a}: p<0.05, ^{aa}: p<0.01; compared to POD 1: ^{b}: p<0.05, ^{bb}: p<0.01; compared to POD 7: ^{c}: p< 0.05, ^{cc} p<0.01; compared to non-R0 en bloc resection: ^{d}: p<0.05, ^{dd}: p<0.01; compared to non-curative R0 resection: ^{e}: p<0.05, ^{ee}: p<0.01.

No significant differences were observed among the three groups before surgery (all p> 0.05), suggesting that patients with different resection types had similar baseline levels of immune and inflammatory status prior to surgery. Postoperatively, compared with the non-R0 en bloc resection group, patients in the non-curative R0 resection group showed significantly lower levels of Treg cells and IL-10, while those in the curative resection group exhibited significantly higher levels of Th1, $CD8^+$, Th1/Th2, and Th1/Th17, alongside lower Treg and IL-10 levels (all p< 0.05). Compared with the non-curative R0 resection group, the curative resection group had higher postoperative Th1 and Th1/Th2 levels and lower Treg and IL-10 levels (all p< 0.05). These findings indicate that R0 resection by ESD was superior to non-R0 en bloc resection in improving postoperative T-lymphocyte subsets and inflammatory markers, and curative resection yielded the most favorable improvement among the three groups.

Additionally, compared with preoperative values, all three groups showed increased levels of Th2, Th17, $CD8^+$, Th17/Treg cell, CRP, IL-6, TNF-α, and IL-10 on POD 1, while Treg cell, Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, and Th1/Th17 levels decreased (all p< 0.05). This indicated that ESD generally induced an acute inflammatory response along with a transient state of immunosuppression in patients, and these changes also existed across all patient groups with different resection types. Relative to POD 1, inflammatory markers (CRP, IL-6, TNF-α, IL-10) declined in a time-dependent manner on POD 7 and 30 in the non-R0 en bloc and curative resection groups. The non-curative R0 resection group exhibited time-dependent decreases in Th2, Th17, CRP, IL-6, TNF-α, and IL-10 on POD 7 and 30 compared to POD 1. Meanwhile, Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, and Th1/Th17 levels increased over time in all groups (all p< 0.05), indicating that postoperative immune parameters were gradually improved, and the inflammatory response gradually resolved.

Overall, these results suggest that curative resection *via* ESD shows superior improvements in postoperative T-lymphocyte subsets and inflammatory markers in patients with early gastrointestinal cancer. This strategy will contribute to significantly superior overall improvement in immune-inflammatory status to non-R0 en bloc resection and non-curative R0 resection.

Further statistical analysis of the incidence of postoperative complications revealed that among patients undergoing non-R0 en bloc resection, non-curative R0 resection, and curative resection, postoperative complications occurred in 15 (46.88%), 7 (11.29%), and 4 (4.21%) patients, respectively (total n = 26, 13.76%). The complications included fever (8, 3, and 3 cases, respectively), postoperative bleeding (2 and 1 cases in the first two groups), nausea and vomiting (3, 2, and 1 cases), perforation (1 case each in non-R0 and non-curative R0 groups), and electrolyte disturbances (1 case in the non-R0 group). The incidence of postoperative complications was significantly higher in the non-R0 en bloc resection group than in the non-curative R0 and curative resection groups, with the curative resection group exhibiting the lowest complication incidence (p<0.001) (Table IV).

Patients were categorized into three groups based on cancer type: EEC group (n=53), EGC group (n=55), and ECC group (n=81). Clinical data, including sex, age, BMI, smoking history, drinking history, family history of gastrointestinal cancer, main lesion size, infiltration depth, differentiation degree, status of horizontal/vertical resection margins (whether clear), vascular invasion, and levels of CA19-9, Hb, WBC, PLT, and NEUT, were analyzed (Table V). The results showed no statistically significant differences in baseline clinical characteristics among the three groups (all p> 0.05).

Dynamic changes in T-lymphocyte subsets and inflammatory markers were compared among patients with varying types of early gastrointestinal cancers pre-ESD and on POD 1, 7, and 30 (Table VI). The results showed that there were no significant differences in T-lymphocyte subsets or inflammatory factors among the three groups preoperatively (all $P > 0.05$), indicating that patients with different types of early gastrointestinal cancer had similar baseline immune-inflammatory status. Also, on POD 1, 7, and 30, no significant

differences were observed among the three groups in T-lymphocyte subsets (Th1, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, Th17/Treg cell, and Th1/Th17) or inflammatory factors (CRP and TNF-α) (all p> 0.05), suggesting that the recovery process of immune-inflammatory status after ESD was basically consistent among different types of early gastrointestinal cancers.

Compared with preoperative levels, all three groups exhibited increases in Th17, Th2, $CD8^+$, Th17/Treg cell ratio, CRP, IL-6, TNF-α, and IL-10 at POD 1, along with decreases in Treg cell, Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, and Th1/Th17 levels (all p< 0.05). Relative to POD 1, these immune cell functions and inflammatory markers, including Th17, CRP, IL-6, TNF-α, and IL-10, declined in a time-dependent manner at POD 7 and 30, while Th1, $CD4^+$, $CD4^+/CD8^+$, Th1/Th2, and Th1/Th17 increased over time (all $P < 0.05$). These results suggest that an immunosuppressive state and acute inflammatory response are present in the early postoperative period following ESD, begin to gradually resolve on POD 7, and return to near-preoperative levels on POD 30, with consistent changes observed across different cancer types.

Table IV. The relationship between ESD resection types and the occurrence of postoperative complications

Postoperative complications	Non-R0 en bloc resection (n = 32)	Non-curative R0 resection (n = 62)	Curative resection (n = 95)	Total (n = 189)	p
	15/17	7/55	4/91	26/163	
Fever (cases)	8	3	3	14	
Postoperative bleeding (cases)	2	1	0	3	
Nausea and vomiting (cases)	3	2	1	6	
Perforation (cases)	1	1	0	2	< 0.001
Electrolyte disorder (cases)	1	0	0	1	
Total (cases)	15	7	4	26	
Incidence of postoperative complications (%)	46.88	11.29	4.21	13.76	

Chi-square test of independence was used to compare the dichotomous variables between groups.

Table V. General clinical data analysis of early gastrointestinal cancer patients

	EEC (n = 53)	EGC (n = 55)	ECC (n = 81)	$z/t/x^2$	p
Age (years)	61 (29, 86)	56 (30, 76)	58 (27, 83)	0.744	0.679
Sex (male/female, cases)	26/27	29/26	43/38	0.232	0.890
BMI (kg/m^2)	22.21 ± 2.27	20.90 ± 1.94	21.91 ± 1.78	1.758	0.175
Smoking history (yes/no, cases)	7/46	13/42	15/66	1.945	0.378
Drinking history (yes/no, cases)	18/35	14/41	18/65	2.309	0.315
Family history of gastrointestinal cancer (yes/no, cases)	11/42	10/45	22/59	1.670	0.434
Main lesion size (cm)	3.10 (1.55, 4.24)	2.99 (1.57, 4.22)	3.05 (1.58, 4.20)	0.301	0.860
Tumor morphology (uplift/flat and depression, cases)	19/34	20/35	29/52	0.005	0.997
Infiltration depth (Mucosal layer/submucosa, cases)	10/43	9/46	7/74	3.268	0.195
Differentiation degree (high and medium differentiation/low differentiation, cases)	52/1	51/4	77/4	1.736	0.420
Horizontal/vertical margin positive (yes/no, cases)	9/44	10/45	14/67	0.030	0.985
Vascular invasion (yes/no, cases)	3/50	2/53	4/77	0.254	0.881
CA19-9 (U/mL)	28.13 (15.24, 62.33)	30.42 (11.23, 81.13)	31.06 (10.57, 87.64)	2.021	0.364
WBC ($10^9/L$)	6.77 (5.04, 15.76)	6.8 (4.8, 12.34)	7.09 (4.65, 16.03)	2.444	0.295
PLT ($10^9/L$)	175.09 (111.47, 375.35)	187.94 (114.57, 310.23)	182.43 (109.21, 390.28)	3.403	0.182
NEUT ($10^9/L$)	5.20 ± 1.37	5.37 ± 1.75	5.32 ± 1.42	0.170	0.844

EEC: early esophageal cancer; EGC: early gastric cancer; ECC: early colorectal cancer; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; WBC: white blood cell; PLT: platelet. Normal distribution test was performed using the Kolmogorov-Smirnov test. Measurement data with normal distribution were expressed as mean ± SD, and one-way ANOVA was used for comparison between groups, followed by Tukey's multiple comparisons test. Measurement data with non-normal distribution were expressed as quartiles, i.e., median (minimum, maximum). Kruskal-Wallis H test was used for comparison between groups, followed by Dunn's multiple comparisons test. Count data were expressed as the number of cases, and the Chi-square test/Chi-Square Goodness-of-Fit Test was used to compare the dichotomous variables between groups.

Table VI. Comparison of T-lymphocyte subsets and inflammatory factors before and after ESD in patients with different types of early gastrointestinal cancer

		EEC (n = 53)	EGC (n = 55)	ECC (n = 81)
Treg (%CD4$^+$T)	Pre-operation	10.11 (8.29, 11.98)	10.11 (7.92, 12.16)	9.95 (8.27, 11.94)
	POD 1	7.59 (6.13, 9.84)^{aa}	7.98 (6.03, 9.98)^{aa}	8.10 (6.21, 9.95)^{aa}
	POD 7	11.82 ± 1.28^{aabb}	11.25 ± 1.27^{aabb}	11.17 ± 1.25^{faabb}
	POD 30	7.86 ± 0.92^{aacc}	8.08 ± 0.98^{aacc}	7.99 ± 0.96^{aacc}
Th1 (%CD4$^+$T)	Pre-operation	14.67 ± 1.98	15.18 ± 2.05	15.22 ± 1.98
	POD 1	13.53 (9.38, 17.00)^{aa}	13.83 (9.06, 16.72)^{aa}	12.91 (8.70, 16.96)^{aa}
	POD 7	17.28 ± 2.34^{aabb}	17.90 ± 2.37^{aabb}	17.12 ± 2.27^{aabb}
	POD 30	22.10 ± 3.19^{aabbcc}	22.27 ± 3.61^{aabbcc}	21.81 ± 2.95^{aabbcc}
Th2 (%CD4$^+$T)	Pre-operation	13.65 (7.86, 17.32)	13.05 (7.18, 16.62)	13.29 (7.41, 17.27)
	POD 1	13.04 (9.82, 20.05)^{aa}	14.32 (10.39, 19.68)^{aa}	16.46 (11.06, 19.95)^{ffggaa}
	POD 7	13.41 ± 1.35^{aa}	13.88 ± 1.34^{aa}	13.58 ± 1.39^{abb}
	POD 30	10.95 (6.23, 13.65)^{aabbcc}	10.69 (6.29, 14.13)^{aabbcc}	10.87 (6.24, 13.59)^{aabbcc}
Th17 (%CD4$^+$T)	Pre-operation	5.16 (2.93, 7.40)	5.30 (2.91, 7.40)	5.26 (2.92, 7.16)
	POD 1	8.04 (5.36, 10.00)^{aa}	7.40 (4.91, 10.11)^{aa}	7.56 (4.92, 10.20)^{faa}
	POD 7	5.48 (3.37, 8.04)^{bb}	5.26 (3.29, 7.62)^{bb}	5.02 (3.33, 7.53)^{b}
	POD 30	4.03 (1.58, 6.14)^{aabbcc}	4.15 (1.59, 6.13)^{aabbcc}	4.26 (1.71, 6.16)^{aabbcc}
CD4$^+$ (%CD3$^+$T)	Pre-operation	33.68 ± 4.72	35.18 ± 4.29	35.84 ± 5.10
	POD 1	30.15 ± 4.23^{aa}	30.46 ± 4.05^{aa}	30.73 ± 4.75^{aa}
	POD 7	32.34 (23.75, 42.32)	33.06 (23.88, 42.54)^{bb}	33.29 (23.94, 45.12)^{bb}
	POD 30	39.81 (28.66, 49.80)^{aabbcc}	39.84 (29.67, 49.83)^{aabbcc}	41.15 (28.43, 50.20)^{aabbcc}
CD8$^+$ (%CD3$^+$T)	Pre-operation	30.06 (24.96, 35.33)	30.36 (25.59, 35.08)	30.74 (25.21, 35.36)
	POD 1	36.61 (31.22, 40.89)^{aa}	36.45 (31.19, 40.25)^{aa}	36.40 (31.01, 40.36)^{aa}
	POD 7	35.05 (32.92, 37.23)^{aa}	35.06 (32.23, 37.30)^{aa}	34.84 (32.65, 36.86)^{aabb}
	POD 30	29.04 ± 2.75^{bbcc}	29.69 ± 2.63^{aabbcc}	29.02 ± 2.69^{aabbcc}
CD4$^+$/CD8$^+$	Pre-operation	1.13 ± 0.19	1.17 ± 0.14	1.19 ± 0.20
	POD 1	0.83 ± 0.13^{aa}	0.85 ± 0.11^{aa}	0.86 ± 0.15^{aa}
	POD 7	0.91 ± 0.14^{aab}	0.95 ± 0.15^{baa}	0.96 ± 0.14^{aab}
	POD 30	1.38 (0.94, 1.91)^{aabbcc}	1.39 (0.89, 1.68)^{bccaa}	1.43 (1.01, 1.95)^{aabbcc}
Th1/Th2	Pre-operation	1.18 (0.73, 2.18)	1.14 (0.72, 2.55)	1.17 (0.72, 2.29)
	POD 1	0.97 ± 0.26^{aa}	0.93 ± 0.20^{aa}	0.80 ± 0.17^{ffggaa}
	POD 7	1.25 (0.94, 2.07)^{aab}	1.31 (0.82, 1.81)^{aabb}	1.24 (0.88, 2.06)^{aabb}
	POD 30	1.97 (1.41, 4.23)^{aabbcc}	1.98 (1.22, 3.49)^{aabbcc}	2.04 (1.16, 4.00)^{aabbcc}
Th17/Treg	Pre-operation	0.51 (0.26, 0.81)	0.49 (0.26, 0.85)	0.49 (0.29, 0.81)
	POD 1	0.99 (0.60, 1.44)^{aa}	0.93 (0.52, 1.43)^{aa}	0.90 (0.52, 1.43)^{aa}
	POD 7	0.47 ± 0.10^{abb}	0.48 ± 0.11^{abb}	0.47 ± 0.12^{abb}
	POD 30	0.52 ± 0.16^{abbcc}	0.50 ± 0.15^{abbc}	0.52 ± 0.17^{abbc}
Th1/Th17	Pre-operation	3.01 (1.93, 5.71)	2.84 (1.70, 6.41)	2.92 (1.83, 6.37)
	POD 1	1.68 (1.04, 2.77)^{aa}	1.73 (0.99, 3.01)^{faa}	1.71 (0.93, 2.97)^{aa}
	POD 7	3.36 (1.82, 5.91)^{aabb}	3.39 (1.90, 6.10)^{aabb}	3.39 (1.81, 5.59)^{aabb}
	POD 30	5.28 (2.76, 16.80)^{aabbcc}	5.68 (2.89, 17.08)^{aabbcc}	5.25 (2.94, 12.11)^{aabbcc}
CRP (mg/L)	Pre-operation	6.88 (4.23, 12.26)	6.96 (2.92, 10.00)	7.46 (1.59, 10.91)
	POD 1	58.43 (36.21, 79.39)^{aa}	53.48 (36.72, 75.88)^{aa}	54.54 (35.15, 82.74)^{aa}
	POD 7	27.77 (7.47, 37.01)^{aabb}	27.93 (7.33, 40.08)^{aabb}	25.10 (8.02, 40.73)^{aabb}
	POD 30	4.11 (1.49, 10.16)^{aabbcc}	4.49 (1.35, 7.99)^{aabbcc}	4.23 (1.29, 15.26)^{aabbcc}
IL-6 (pg/mL)	Pre-operation	4.30 (1.53, 6.39)	4.15 (1.49, 7.04)	3.83 (0.93, 6.81)
	POD 1	130.20 ± 40.87^{aa}	128.00 ± 35.18^{aa}	136.20 ± 35.15^{aa}
	POD 7	25.61 (10.23, 73.84)^{aabb}	26.12 (10.23, 56.70)^{aabb}	31.59 (10.73, 59.93)^{faabb}
	POD 30	3.16 (0.79, 6.81)^{aabbcc}	4.16 (0.89, 7.13)^{bbcc}	3.25 (0.76, 7.06)^{aabbcc}

Table VI (continued)				
TNF-α (pg/mL)	Pre-operation	4.48 ± 1.41	4.38 ± 1.67	4.36 ± 1.59
	POD 1	75.17 ± 21.88^{aa}	72.90 ± 21.43^{aa}	76.04 ± 20.03^{aa}
	POD 7	20.54 (8.82, 58.33)^{aabb}	21.00 (8.08, 44.79)^{aabb}	23.59 (8.08, 47.34)^{aabb}
	POD 30	3.41 (0.82, 7.18)^{aabbcc}	4.41 (0.96, 7.50)^{aabbcc}	3.55 (1.50, 7.70)^{aabbcc}
IL-10 (pg/mL)	Pre-operation	13.14 (8.89, 15.55)	12.67 (8.81, 15.49)	13.36 (8.71, 15.62)
	POD 1	23.27 (15.66, 34.31)^{aa}	25.42 (15.43, 35.79)^{aa}	27.78 (16.27, 34.72)^{faa}
	POD 7	18.56 ± 4.02^{aabb}	19.41 ± 3.23^{aabb}	16.70 ± 3.42^{ffggaabb}
	POD 30	9.78 (6.95, 15.24)^{aabbcc}	10.26 (6.88, 14.53)^{aabbcc}	10.07 (6.79, 18.58)^{aabbcc}

For abbreviations see Table I and II. Normal distribution test was performed using the Kolmogorov-Smirnov test. Measurement data with normal distribution were expressed as mean ± SD, and one-way ANOVA was used for comparison between groups, followed by Tukey's multiple comparisons test. Measurement data with non-normal distribution were expressed as quartiles, i.e., median (minimum, maximum). Kruskal-Wallis H test was used for comparisons among multiple groups, followed by Dunn's multiple comparisons test. Compared to preoperative day 1: ^{a}: p<0.05, ^{aa}: p<0.01; compared to POD 1: ^{b}: p<0.05, ^{bb}: p<0.01; compared to POD 7: ^{c}: p<0.05, ^{cc}: p<0.01; compared to EEC: ^{f}: p<0.05, ^{ff}: p<0.01; compared to EGC: ^{g}: p<0.05, ^{gg}: p< 0.01.

As shown in Table VI, postoperative complications occurred in 9 patients with EEC (4 with fever, 2 with postoperative bleeding, 2 with nausea and vomiting, 2 with perforation, 1 with electrolyte disorder; complication rate 20.75%), 7 patients with EGC (5 with fever, 2 with nausea and vomiting; complication rate 12.73%), and 8 patients with ECC (5 with fever, 1 with postoperative bleeding, 2 with nausea and vomiting; complication rate 9.88%), totaling 26 cases (12.87%). There was no significant difference in the incidence of postoperative complications among patients with EEC, EGC, and ECC (p> 0.05) (Table VII).

DISCUSSION

Endoscopic submucosal dissection is a minimally invasive procedure commonly employed for the management of early gastrointestinal cancers (including ECC, EGC, and EEC), providing high en bloc resection rates and low local recurrence [44, 45]. While its technical efficacy is well-established, the systemic immunological impact of ESD, particularly across different resection types, remains incompletely understood. Lymphocyte subsets and inflammatory cytokines are key regulators of immune system function and inflammation [46, 47]. Therefore, this study investigated the dynamic changes in inflammatory markers and T-lymphocyte subsets following ESD, stratified by resection curability. Our findings demonstrated that ESD was associated with improved postoperative immune profiles and reduced inflammation in early gastrointestinal cancer. Notably, patients who achieved curative resection exhibited the most favorable immunological recovery, characterized by improved T-lymphocyte subset profiles, reduced inflammatory cytokine levels, and the lowest incidence of postoperative complications.

Baseline tumor size exhibits a statistically significant relationship with systemic inflammation response in gastrointestinal cancers such as gastric cancer [48]. Patients with early gastrointestinal cancers often present preoperatively with a chronic inflammatory microenvironment and immunosuppression, characterized by elevated pro-inflammatory cytokines and reduced $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ ratios, which are associated with impaired immune surveillance [49, 50]. In the present study, perioperative immune-inflammatory alterations were closely associated with tumor characteristics derived from imaging techniques and EUS, an optimal pre-treatment modality for assessing lesion origin, size, echogenicity, and depth of wall invasion

Table VII. Patients with different types of early gastrointestinal cancer and their postoperative complication occurrence

	EEC (n = 53)	EGC (n = 55)	ECC (n = 81)	Total (n = 189)	p
Postoperative complication	11/42	7/48	8/73	26/163	
Fever (cases)	4	5	5	14	
Postoperative bleeding (cases)	2	0	1	3	0.613
Nausea and vomiting (cases)	2	2	2	6	
Perforation (cases)	2	0	0	2	
Electrolyte disorder (cases)	1	0	0	1	
Total (cases)	11	7	8	26	26
Incidence of postoperative complications (%)	20.75%	12.73%	9.88%	13.76%	12.87%

For abbreviations see Table V. Chi-square test of independence was used to compare the dichotomous variables between groups.

[51]. Studies have also linked baseline tumor burden and lesion size to tumor response to immunotherapeutics [52, 53]. Consistently, patients with larger lesions (> 3.04 cm) in this research exhibited more pronounced immunosuppression and inflammatory responses before and shortly after ESD. In addition, flat or depressed lesions were associated with aggravated postoperative inflammatory responses and slower immune recovery compared with protruding lesions. Coherently, deeper tumor invasion (submucosal invasion) resulted in more persistent immunosuppression and inflammation. Collectively, these results indicate that preoperative lesion size, morphology, and invasion depth substantially influence both baseline immune status and immune recovery post-ESD.

Surgical stress can facilitate cancer metastasis, partly through the suppression of anti-tumor immunity [54]. Treg cells can inhibit anti-tumor effector cells, including Tc cells and natural killer cells, which contribute to postoperative immunosuppression and the development of a premetastatic niche [55]. Alterations in T-lymphocyte subsets, characterized by decreased $CD3^+$ and $CD4^+$ T cells, increased $CD8^+$ T cells, and a reduced $CD4^+/CD8^+$ ratio, reflecting an immunosuppressive state in tumor patients [56]. IL-1β, IL-6, and TNF-α are the primary pro-inflammatory cytokines associated with strictures following ESD [57]. In this study, the immunological dynamics post-ESD showed a transient disturbance followed by systemic recovery. Similarly, the esophageal mucosal defect resulting from ESD first elicits an inflammatory response and then initiates a wound-repair process [17]. We found that an initial acute phase (POD 1) exhibited elevated levels of inflammatory markers (CRP, IL-6, and TNF-α), increased Th2/Th17 activity, and reduced Treg cell levels, indicating surgical stress, which partially echoes previous studies [58, 59]. Subsequently, a clear recovery phase emerged (POD 7 and 30), with time-dependent decreases in inflammatory cytokines alongside progressive restoration of cellular immunity. Meanwhile, the rise in Treg cell levels on POD 7, followed by a decline toward baseline levels on POD 30, may reflect a feedback mechanism to temper the initial inflammation and re-establish immune homeostasis. On POD 1 after ESD, inflammatory responses may increase due to mechanical injury, whereas from POD 7 – 30, with mucosal healing and elimination of tumor-derived stimuli, the levels of inflammatory cytokines are declined, and the balance between T-cell subsets will be gradually recovered. These coordinated shifts suggest that ESD facilitates a transition from post-procedural inflammation to a restored, Th1-polarized immune homeostasis, potentially contributing to improved clinical recovery.

Consistent with previous findings [60], curative resection was related to greater reductions in inflammatory markers and better immune reconstruction than non-curative R0 resection and non-R0 en bloc resection in this study. Importantly, curative resection can eliminate tumor-driven inflammatory–immune dysregulation [61], likely by removing the abnormal immune microenvironment, reducing systemic inflammatory burden, and restoring immune homeostasis [61, 62]. In contrast, non-R0 resection, at a higher risk of tumor residue and greater procedural trauma, may result in persistent inflammation and delayed immune recovery [63]. In this study, curative resection contributed to a lower incidence of clinical postoperative complications than non-R0 resection. The pro-inflammatory marker, TNF-α, is associated with worsen postoperative inflammation and delayed wound healing [64, 65]. Excessive inflammation and immune imbalance represent important mechanisms underlying postoperative complications, whereas curative resection may mitigate inflammation and accelerate mucosal repair [66, 67]. Surgical trauma can activate damage-associated molecular patterns, thereby triggering a pro-inflammatory cytokine surge and subsequent immune paralysis [68], which may partly explain persistent low-grade fever and delayed wound healing in some patients after surgery. Thus, monitoring inflammatory cytokines and T-cell subsets may therefore help identify high-risk patients at an early stage. Overall, this study reveals that ESD contributes to the improvement of postoperative inflammatory and immune disturbances, and curative resection appears crucial for promoting recovery and reducing complications. Additionally, dynamic monitoring of inflammatory and immune markers may also provide valuable information for evaluating postoperative recovery and optimizing follow-up strategies. Further, insignificant differences in postoperative inflammatory or immune changes across early esophageal, gastric, and colorectal cancers suggest that the inflammatory-immune response after ESD is largely organ-independent, supporting a unified postoperative immune-inflammatory monitoring strategy.

The complexity of an ESD procedure can be influenced by factors such as the location and size of the lesion, anatomical factors, the surgeon's experience, and patient cooperation levels [69]. Previous research suggests that the gastric neoplasms' location may influence both the extent of resection and the incidence of post-ESD complications [70, 71]. By contrast, we found that patients with EEC, EGC, and ECC showed comparable baseline profiles and similar postoperative changes in Tlymphocyte subsets and inflammatory markers, with no significant difference in complication rates. This discrepancy may arise because we only focus on early-stage tumors, and our analysis spanned multiple organs (esophagus, stomach, and colon) - a broader anatomical range than prior research focused on intragastric location alone. Consequently, the type of resection (R0 and curative status) emerges as a more potent and universal modulator of postoperative recovery than the specific tumor location within the gastrointestinal tract.

This study has several limitations. The sample size of this study remains relatively limited, and larger cohorts will be needed in future investigations to validate these findings. Moreover, the study focused primarily on short-term postoperative dynamics and lacked long-term follow-up, making it impossible to determine whether changes in immune and inflammatory markers influence long-term outcomes such as recurrence or survival. Additionally, this study mainly described phenotypic changes without exploring the underlying molecular mechanisms, including signaling pathway activation or cytokine network regulation.

Follow-up over several months or longer may help clarify the relationship between postoperative immune-inflammatory dynamics, long-term quality of life, and tumor recurrence risk. In addition, mechanistic studies integrating transcriptomics,

proteomics, and related approaches will be conducted to explore the molecular basis underlying site-specific immune responses after ESD, with the aim of identifying potential biomarkers and therapeutic targets.

CONCLUSIONS

This study is the first to systematically characterize the dynamic changes in inflammatory cytokines and T-lymphocyte subsets following ESD in patients with early gastrointestinal cancers originating from different anatomical sites (esophagus, stomach, and colorectum). By integrating postoperative inflammatory markers with key immunological indicators, such as $CD4^+$ and $CD8^+$ T cells and the $CD4^+/CD8^+$ ratio, this study provides a comprehensive dynamic evaluation of the postoperative immune–inflammatory state, contributing to a deeper understanding of how ESD influences immune homeostasis. Future work will involve multicenter studies with extended follow-up and incorporation of more diverse clinical endpoints.

Conflicts of interest: None to declare.

Authors' contribution: L.H. was responsible for study concepts, study design and manuscript review. L.H., P.W. and Z.B. contributed to the data acquisition. P.W., Z.B. and X.Q. contributed to literature research, and statistical analysis. L.H. was responsible for ensuring the integrity of the entire research and the definition of the knowledge content. All authors read and approved the final manuscript.

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