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Efficacy of current therapeutic strategies for immune checkpoint inhibitor-related esophagitis

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Abstract

Background Immune checkpoint inhibitor-related esophagitis (IME) is often managed with proton pump inhibitors (PPIs). Severe or refractory cases may require steroids and/or selective immunosuppressive therapies (SIT). However, large-scale studies assessing IME treatment strategies are lacking. This study evaluated their efficacy.

Method This retrospective study at a tertiary cancer center included patients with malignancy who received immune checkpoint inhibitor (ICIs) from 2010-2024 and developed IME, defined as new or worsening upper gastrointestinal (GI) symptoms post-ICI initiation with other causes excluded.

Results Among 148 patients, 75% received PD-1/PD-L1 inhibitors for 4.9 months; 50.7% received concurrent chemotherapy. Isolated IME was present in 27.7% of patients, while the remainder had concurrent immune-mediated GI conditions. Only 24.4% of isolated IME cases were treated with PPIs, and there was no significant difference between the PPI and non-PPI groups in steroid administration, outcomes or recurrence. Corticosteroids were used in 27.7% of cases, significantly shortening the time to symptom resolution (12 vs. 45 days; P=0.015). Nausea (87.8% vs. 57%, P<0.001) and emesis (58.5% vs. 34.6%, P=0.008) were more frequently observed in the steroid group, along with higher rates of hospitalization (73.2% vs. 36.4%, P<0.001), need for intravenous steroids (30% vs. 0%, P<0.001), and ICI discontinuation (74.4% vs. 44.6%, P=0.002). SIT were required for other concomitant GI adverse events in 41.5% of the steroid-treated patients. No significant differences in clinical improvement, ICI resumption or all-cause mortality were noted between the corticosteroid and non-corticosteroid groups.

Conclusion Our findings showed faster clinical improvement with steroids, while PPIs demonstrated no significant effectiveness.

Keywords Immune checkpoint inhibitors, proton pump inhibitors, corticosteroids, budesonide, immune checkpoint inhibitor-related esophagitis

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Introduction

Cancer cells evade immune surveillance by exploiting immune modulatory receptors that trigger inhibitory signals, which dampen the host's natural antitumor response. These receptors are blocked by immune checkpoint inhibitors (ICIs), such as anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thereby restoring the immune system's ability to target malignancies [1]. However, this therapeutic strategy can lead to immune overactivation, which may disrupt self-tolerance [2] and increase diversification in

Conflict of Interest: None

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the T-cell repertoire, potentially contributing to autoimmune reactions known as immune-related adverse events (irAEs) [1]. Among these, upper gastrointestinal (GI) toxicity is uncommon, with an estimated incidence of 3% [3].

Immune checkpoint inhibitor-related esophagitis (IME) typically develops within 4 months of ICI initiation, presenting with nausea, vomiting, dysphagia and hematemesis. In a study of the largest cohort with this toxicity to date, the median duration of symptoms was approximately 30 days [3]. The diagnosis of IME is confirmed using esophagogastroduodenoscopy (EGD), with biopsies from multiple esophageal sites, along with the exclusion of infectious causes—similar to the evaluation of lower GI adverse effects [4]. EGD typically reveals multifocal non-ulcerative inflammation, but isolated inflammation of the middle third of the esophagus is also common. Histological examination shows chronic active or acute active inflammation, at similar rates [3].

Anti-PD-1/PD-L1 inhibitors are the most common cause of upper GI toxicity, accounting for 71-85% of cases [3,5]. While preexisting autoimmune disease is present in only 8% of patients with IME [6], a history of non-steroidal anti-inflammatory use, smoking, radiotherapy, and the use of proton pump inhibitors (PPIs) or histamine 2 receptor (H_2) blockers, is more frequently reported [3,6]. Current guidelines provide no specific management recommendations for this condition, deferring to clinicians' expertise. A retrospective review by Panneerselvam *et al* found that treatment primarily consisted of PPIs in 67% of cases, with corticosteroids used less frequently (19%). Selective immunosuppressive therapy (SIT) was administered exclusively to patients with concurrent immune-mediated diarrhea and colitis (IMDC). Among symptomatic patients, 88.2% experienced symptom resolution after treatment, and 4 of 5 patients who underwent repeat EGD showed endoscopic remission [3]. While IME is generally mild, severe cases can lead to complications such as stenosis [7] and fistulization [8].

As immunotherapy becomes a standard treatment for malignancies, the incidence of irAEs, including IME, is expected to rise. To date, IME has been described primarily in case reports and small case series, with the largest study including only 21 patients and limited descriptive data. This study aimed to evaluate the efficacy of current management strategies, assess their impact on overall survival outcomes, and identify risk factors for IME. Additionally, the study sought to more comprehensively describe the clinical, endoscopic, and histological features of IME.

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Patients and methods

Study design

This retrospective study, conducted at a tertiary cancer center, included patients who received ICIs for malignancy and underwent EGD to assess upper GI toxicity during the period January 2010 through June 2024, based on the electronic health record. The inclusion criteria required patients to have presented with new-onset or worsened preexisting symptoms of IME, and immune-related esophageal inflammation caused by an overstimulated immune system that had lost central and peripheral tolerance in the context of ICI therapy. Excluded were those with an alternative etiology for their esophagitis, such as infectious causes, malignancy, autoimmune disorders, gastroesophageal reflux disease (GERD), drug-induced-esophagitis, or radiation-related injury confirmed by histology (Fig. 1). Demographic data, endoscopic and histological findings, treatment details, and clinical outcomes were collected for all eligible patients.

Ethics approval and consent

Ethics approval was granted by the MD Anderson Institutional Review Board (PA18-0472) with a waiver of consent.

IME clinical characteristics and outcomes

Baseline demographic data, as well as oncology-related and IME-related variables, were collected and analyzed. The clinical severity of IME was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 grading system. Primary outcomes were clinical and endoscopic improvement or remission, symptom duration, and hospitalization rates. Secondary outcomes comprised changes in the frequency, dose and class of PPIs, as well as the use, route of administration, class and duration of corticosteroids.

EGD evaluation

Endoscopy findings were categorized into normal mucosa, non-ulcerative inflammation, ulcerative inflammation, or hemorrhage/spontaneous bleeding, located in the upper, middle or lower third of the esophagus (Fig. 2). Histological findings were classified as normal, acute active inflammation (apoptosis, increased eosinophils, neutrophils, cryptitis, crypt

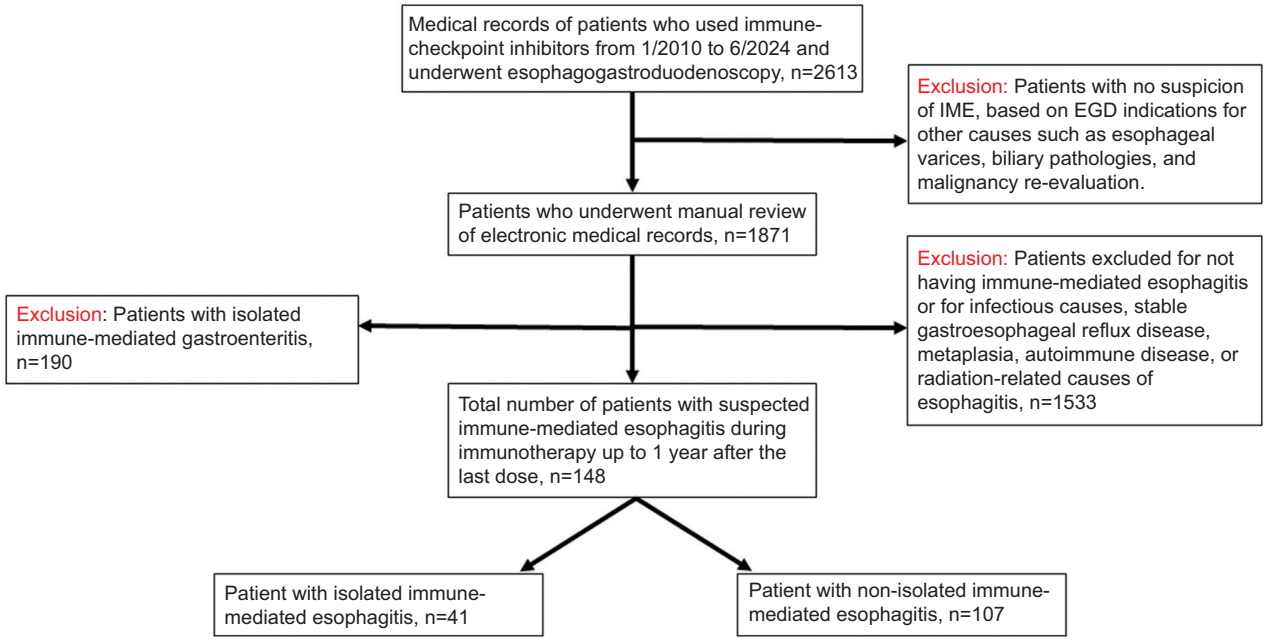

Figure 1 Flow chart for patient selection in immune checkpoint inhibitor-related esophagitis
EGD, esophagogastroduodenoscopy; IME, immune checkpoint inhibitor-related esophagitis

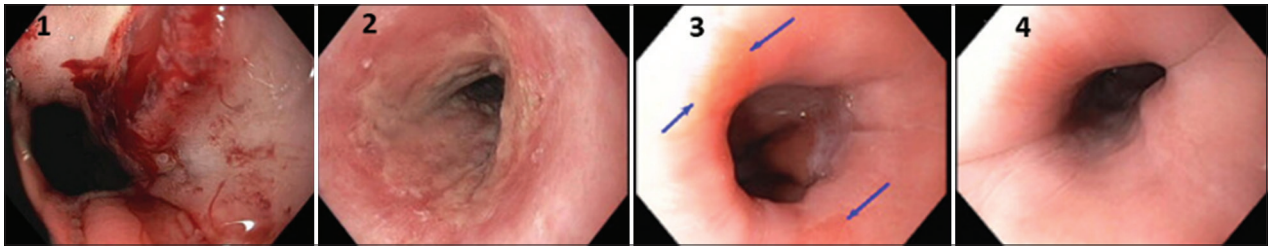

Figure 2 Esophagogastroduodenoscopy findings. (1) Spontaneous bleeding. (2) Ulcerative inflammation. (3) Non-ulcerative inflammation (patchy erythema), indicated by arrows. (4) Normal mucosa

abscess), chronic active inflammation (crypt distortion, basal lymphoplasmocytosis, Paneth cell metaplasia, or chronic active inflammation), chronic inactive inflammation (lymphocytes and plasma cells, with minimal to absent neutrophilic activity and no evidence of active epithelial injury, ulceration, or necrosis, reflecting prior inflammatory insult with residual immune cell infiltration), or chemical (non-radiation-related) reactive changes (non-neoplastic epithelial alterations secondary to chemical or irritative injury, with regenerative atypia and nuclear enlargement with preserved polarity). Time from the onset of IME symptoms to endoscopy was also recorded.

Statistical analysis

The statistical analysis was performed using SPSS version 24.0. Continuous variables were summarized by their medians and interquartile ranges (IQRs), while categorical variables were summarized by their frequencies and percentages. The chi-square test (2-sided, with Pearson's correction) was used to compare 2 categorical variables. The Mann–Whitney *U* test was used to compare the distributions of 2 continuous variables. Univariate binary logistic regression analysis was conducted to investigate the association between various risk factors and the development of isolated IME. Univariate binary logistic regression was also used to examine the relationship between various clinical practices and symptom improvement or remission.

Results

Patients' demographic and clinical characteristics

A total of 148 patients met the inclusion criteria, with an IME incidence of 5.6%. The cohort was predominantly white (75.7%) and male (57.4%), with a median age of 64.9 years. Common cancer types included lung (25%), genitourinary (21.6%), and GI (18.9%). At the time of toxicity, 62.2% had stage IV cancer, and 58.8% had an Eastern Cooperative

Oncology Group performance status of 1. Regarding ICIs, most received anti-PD-1/PD-L1 agents (75%), while 22.3% received combined ICI regimens, and 2.7% received isolated anti-CTLA-4 therapy. Concurrent chemotherapy was administered to 50.7%, with 69.3% of them receiving agents potentially associated with upper GI toxicity. Among patients with isolated IME (41, 27.7%), i.e. without co-occurrence of other GI irAEs, 18 (43.9%) received chemotherapy concurrently with ICI; only 5 (27.8%) of them received known esophagitis-associated agents. A smoking history was recorded for 48.6%, as was the use of nonsteroidal anti-inflammatory drugs (12.2%), PPIs (34.5%), and H_2 blockers (8.1%). Comorbidities included GERD (58.1%) and prior radiation to the abdomen, lungs or breast (16.9%), administered a median of 116 days before the onset of upper GI toxicity symptoms. Patients were followed for a median of 0.8 years, with an all-cause mortality rate of 45.3% (Table 1).

Table 1 Demographic characteristics of patients with immune checkpoint inhibitor-related esophagitis, n=148

Characteristics	No. (%)
Age at the time of immunotherapy, *median (IQR), years*	64.9 (56.2-72.7)
Male sex	85 (57.4)
White race	112 (75.7)
Type of ICI	
Anti-PD-1/PD-L1 agent	111 (75)
Anti-CTLA-4 agent	4 (2.7)
Combination	33 (22.3)
Duration of immunotherapy, *median (IQR), months*	7.6 (1.6-18.3)
Chemotherapy concurrent with ICI	75 (50.7)
Agents associated with esophagitis[1]	52 (69.3)
Agents not associated with esophagitis	23 (30.7)
Chemotherapy concurrent with ICI for isolated IME	18 (43.9)
Agents associated with esophagitis[1], n=18	5 (27.8)
Agents not associated with esophagitis, n=18	13 (72.2)
Cancer type	
Lung	37 (25)
Genitourinary	32 (21.6)
Gastrointestinal	28 (18.9)
Melanoma	25 (16.9)
Head and neck	10 (6.8)
Other	16 (10.9)
Cancer stage	
I	2 (1.4)
II	10 (6.8)
III	29 (19.6)
IV	92 (62.2)
ECOG	
0	31 (20.9)
1	87 (58.8)
2-4	30 (20.3)
Medical history and comorbidities	
GERD	86 (58.1)
Ever smoker	72 (48.6)
PPI use	51 (34.5)
Radiation[2]	25 (16.9)
NSAID use	18 (12.2)
H_2 blocker use	12 (8.1)
All-cause mortality	67 (45.3)
Length of follow up, *median (IQR), years*[3]	0.8 (0.3-2.1)

[1]Included platinum analogs, alkylating agents, anthracyclines, antimetabolites, taxanes and vinca alkaloids
[2]In abdominal, lung, and breast regions
[3]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death
CTLA-4, cytotoxic T-lymphocyte antigen 4; ECOG, Eastern Clinical Oncology Group performance status; GERD, gastroesophageal reflux disease; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PD-1/PD-L1, programmed cell death 1/programmed cell death ligand 1; PPI, proton pump inhibitor

Clinical features of IME

IME developed a median of 4.9 months after ICI initiation. The most common symptoms were nausea (65.5%), emesis (41.2%), epigastric pain (34.5%), dysphagia (33.1%), acid reflux (28.4%), and odynophagia (8.8%). Sixty-eight cases were grade 1, 72 were grade 2, and 8 were grade 3. IME was isolated in 27.7% of patients, while 50.7% had concurrent immune-mediated gastroenteritis (IMG) and 15.5% had both IMG and IMDC. Among 88 patients on PPIs, 36.4% started after diagnosis; of those with prior PPI use, 38% underwent regimen modifications, including dose escalation (16%) and class switch (22%). Sucralfate was prescribed in 28.4% of cases. Corticosteroids were administered to 27.7% of patients, with 17.6% receiving prednisone and 6.1% receiving budesonide, for a median of 43 days. SIT was required in 12.8%, with a median of 2 doses. Hospitalization occurred in 46.6% of patients, with a median stay of 7 days; 6.1% required intravenous corticosteroids. Clinical improvement/remission was observed in 60.1%, with a median symptom duration of 30 days. ICIs were successfully resumed in 53.1% of those who initially discontinued therapy (Table 2).

Univariate binary logistic regression analysis of risk factors for isolated IME development compared with those with upper GI toxicity

Data on IMG were included for this particular analysis, following the same inclusion and exclusion criteria, with IMG as the primary diagnosis. For the univariate analysis, the control group comprised patients with upper GI toxicity excluding isolated IME. Risk factors associated with isolated IME are shown in Table 3. Prior abdominal, lung or breast radiotherapy was significantly associated with isolated IME (odds ratio [OR] 3.1, 95% confidence interval [CI] 1.6-6.3;

Table 2 Clinical features among patients with immune checkpoint inhibitor-related esophagitis, n=148

Characteristics	No. (%)
Time from ICI to IME, *median (IQR), months*	4.9 (2.2-10)
CTCAE grade for esophagitis	
0-1	68 (43.2)
2 and above	80 (54)
Presenting symptoms	
Nausea	97 (65.5)
Emesis	61 (41.2)
Epigastric pain	51 (34.5)
Dysphagia	49 (33.1)
Acid reflux	42 (28.4)
Early satiety	20 (13.5)
Odynophagia	13 (8.8)
Melena	13 (8.8)
Belching	1 (0.7)
Isolated IME and IME combinations with IMG and IMDC	
Isolated IME	41 (27.7)
Co-occurrence of IME and IMG	75 (50.7)
Co-occurrence of IME, IMG, and IMDC	23 (15.5)
Incidence of complications[1]	9 (6.1)
Endoscopic interventions	
Endoclips	4 (2.7)
Cauterization	2 (1.4)
Dilation	4 (2.7)
Treatment	
PPI administration without prior use[2], n=88	32 (36.4)
PPI regimen modification[3], n=50	19 (38)
Dose escalation	8 (16)
Class modification	11 (22)
H_2 blocker administration without prior use[2], n=128	7 (5.4)
H_2 blocker regimen modification3, n=12	1 (8.3)
Dose escalation	0 (0)
Class modification	1 (8.3)
Sucralfate administration	42 (28.4)
Steroid administration	41 (27.7)
Prednisone	26 (17.6)
Budesonide	9 (6.1)
Time from IME onset to steroid use, *median (IQR), days*	5 (0-20)
Duration of steroid treatment, median (IQR), *days*	43 (19.5-97.7)
Intravenous steroids needed	9 (6.1)
SIT[4]	19 (12.8)
Time from IME onset to SIT use, *median (IQR), days*	12 (3-50)
Multiple SIT agents used, n=19	10 (52.6)
Number of SIT doses, *median (IQR)*	2 (1-4)
Outcomes	
Clinical improvement/remission	89 (60.1)
Persistent symptoms for 6 months	11 (7.4)
Duration of IME symptoms, median (IQR), days	30 (10-72)
Hospitalization for IME	69 (46.6)
Length of hospitalization, median (IQR), days	7 (3-10)
Multiple hospitalizations, n=69	19 (27.5)
ICI held	64 (45.7)
ICI resumed, n=64	34 (53.1)
IME recurrence after ICI resumption	10 (6.8)
All-cause mortality	67 (45.3)
Length of follow up[5], *median (IQR), years*	0.8 (0.3-2.1)

[1]Complications included esophageal stricture, fistulization, requirement for feeding tube insertion or percutaneous endoscopic gastrostomy tube placement
[2]Included patients without prior use of PPIs or H_2 blockers
[3]Included patients who had used PPIs prior to the onset of IME
[4]SITs used to treat esophagitis include infliximab, vedolizumab, and ustekinumab
[5]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death
CTCAE, Common Terminology Criteria for Adverse Events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; IMC, immune-mediated diarrhea and colitis; IME, immune checkpoint inhibitor-related esophagitis; IMG, immune-mediated gastroenteritis; IQR, interquartile range; PPI, proton pump inhibitor; SIT, selective immunosuppressive therapy

Table 3 Univariate analysis of factors potentially associated with isolated immune checkpoint inhibitor-related esophagitis among patients who developed upper gastrointestinal toxicity, n=449

Factors	Odds ratio (95% confidence Interval)	P-value
Cancer type: melanoma vs. others	0.4 (0.1-1.2)	0.124
Stage: III-IV vs I-II	0.7 (0.2-1.9)	0.494
Number of ICI cycles	0.9 (0.9-1.02)	0.735
PD-1/PD-L1 vs. CTLA-4 ± PD-1/PD-L1 inhibitor	2.4 (0.9-5.9)	0.051
Chemotherapy[1] association: yes vs. no	1.3 (0.4-3.6)	0.591
Radiation: yes vs. no	3.1 (1.6-6.3)	0.001
Ever smoker: yes vs. no	0.9 (0.4-1.7)	0.767
GERD: yes vs. no	1.6 (0.8-3.1)	0.147
Baseline NSAID use: yes vs. no	0.2 (0.06-1.1)	0.074
Baseline PPI use: yes vs. no	1.5 (0.8-3.0)	0.193

[1]Included platinum analogs, alkylating agents, anthracyclines, antimetabolites, taxanes and vinca alkaloids
CTCAE, common terminology criteria for adverse events; GERD, gastroesophageal reflux disease; ICI, immune checkpoint inhibitor; IME, immune checkpoint inhibitor-related esophagitis; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PD-1/PD-L1, programmed cell death 1/programmed cell death ligand 1

P=0.001), with a potential association seen for PD-1/PD-L1 therapy (OR 2.4, 95%CI 0.9-5.9; P=0.051).

Endoscopic and histological features

The median time between IME onset and EGD was 3 days. EGD revealed non-ulcerative inflammation in 54.7% and ulcerative inflammation in 14.2%. The lower third of the esophagus was most commonly affected (56.1%), followed by the middle third (21.6%) and upper third (20.9%). Histology most commonly showed acute inflammation (28.4%), chemical reactive changes (22.3%), chronic inflammation (12.2%) or chronic inactive inflammation (6.1%). Of the 33 patients with chemically reactive changes, 9 were also receiving chemotherapeutic agents known to potentially induce esophagitis (Supplementary Table 1).

Comparison of IME clinical features according to PPI use

A comparison of clinical features and outcomes between patients with isolated IME who received PPIs and those who did not revealed no significant differences overall. Nonetheless, a higher proportion of patients with CTCAE grade 2 or above for IME were prescribed PPIs (77.8% vs. 45.2%, P=0.085). The patients who received PPIs did not significantly differ from those who did not in terms of clinical improvement or remission rate (70% vs. 57.1%, P=0.475), median symptom duration (54 vs. 30 days, P=0.781), hospitalization rates (50% vs. 35.5%, P=0.413), or resumption of ICI (50% vs. 47.4%, P=0.924) among those who had discontinued therapy. Moreover, there were no differences in all-cause mortality (60% vs. 48.4%, P=0.523) or length of follow up (1.4 vs. 0.6 years, P=0.404) (Supplementary Table 2). A comparison of clinical features and outcomes between patients with isolated IME who received H_2 blockers and those who did not also revealed no significant differences overall (Supplementary Table 3).

Comparison of IME clinical features according to corticosteroid use

Comparison between IME patients who received corticosteroids and those who did not revealed mild differences. The corticosteroid group (CG) had a higher hospitalization rate (73.2% vs. 36.4%, P<0.001) and greater SIT use (41.5% vs. 0%, P<0.001), though their length of stay was similar (7 vs. 7 days, P=0.956). Clinical improvement/remission rates were comparable (71.8% vs. 59.8%, P=0.187), but symptom duration was shorter in the CG (12 vs. 45 days, P=0.015). Symptom recurrence within 6 months was more frequent in the CG (14.3% vs. 5.3%, P=0.087), though the difference was not statistically significant. All-cause mortality (36.6% vs. 48.6%, P=0.189) and follow-up duration (0.6 years vs. 0.9 years, P=0.898) were similar (Table 4). Subgroup analysis of isolated IME patients showed that the CG had a higher hospitalization rate (71.4% vs. 32.4%, P=0.054) (Supplementary Table 4).

Univariate binary logistic regression analysis of factors associated with clinical improvement among patients with isolated IME

In univariate and subsequent multivariate analysis, clinical improvement or remission showed no significant associations with corticosteroid treatment, PPI or H_2 blocker use, and ICI discontinuation during the index event (Supplementary Tables 5, 6).

Discussion

Among patients at a tertiary cancer center who received ICIs and underwent an EGD in the past 14 years, IME incidence was 5.6%—an increase from the 3% reported in 2021 [3], reflecting the expanded use of immunotherapy. This study refines the current clinical understanding of IME and demonstrates that corticosteroids led to faster clinical improvement, while PPIs offered no significant benefit. Only a small subset of patients in our study who developed IME were also receiving chemotherapy agents linked to esophagitis, suggesting that combining immunotherapy and traditional treatments has low impact on esophageal toxicity. Finally, a history of smoking [3] was still frequent among our cohort.

Prior radiotherapy led to a higher incidence of isolated IME, consistent with evidence that combining radiotherapy and immunotherapy increases the frequency, but not the severity, of adverse effects [9,10]. Radiotherapy promotes tumor cell death through DNA damage and modulates immune system activity by upregulating MHC class I [11,12], PD-1/PD-L1 expression [13-15], and tumor-infiltrating lymphocyte density [14], while also activating dendritic cells. These effects sensitize tumors and create synergy with ICIs [16], contributing to increased remission rates, via the abscopal effect [17,18], and better treatment outcomes [16,19], as currently under evaluation in clinical trials [20]. This immune interaction [21,22] with ICIs may underlie the greater incidence of isolated IME with radiotherapy, warranting further investigation.

Chemoradiotherapy, which targets rapidly proliferating cells, can inadvertently damage GI mucosa, trigger pyloric spasm, and relax the lower esophageal sphincter—contributing to gastric content buildup and reflux. In such cases, PPIs are often prescribed to relieve heartburn or epigastric pain by raising stomach pH and protecting mucosa [23]. However, long-term PPI use increases the risk of *Clostridioides difficile* and respiratory tract infections; deficiencies in vitamin B12, magnesium, and calcium; rebound hypersecretion; and gastric malignancies [24,25]. In cancer patients, PPI use warrants further caution [26,27], as gastric alkalinization can reduce chemotherapeutic bioavailability [28]; modify the gut microbiome [29], which contributes to IMDC; potentially lead to immune-mediated nephritis [30]; and impair the efficacy of

Table 4 Clinical features and outcomes among patients with immune checkpoint inhibitor-related esophagitis treated with steroids vs. those not treated with steroids, n=148

Feature/outcome	No. (%)		
	No steroid treatment, n=107	Steroid treatment, n=41	P-value
Time from ICI to IME, *median (IQR), months*	5.1 (2.3-11.2)	4.5 (2.2-9.4)	0.995
Length of ICI, *median (IQR), months*	8.7 (2.9-18.7)	4.9 (1.8-14)	0.128
Type of ICI			
Anti-CTLA-4	4 (3.7)	0 (0)	0.209
Anti-PD-1/PD-L1	87 (81.3)	24 (58.5)	0.004
Combination	16 (15)	17 (41.5)	0.001
CTCAE grade for esophagitis			
0-1	50 (46.7)	18 (43.9)	0.757
2 and above	57 (53.3)	23 (56.1)	
Presenting symptoms			
Nausea	61 (57)	36 (87.8)	<0.001
Emesis	37 (34.6)	24 (58.5)	0.008
Acid reflux	34 (31.8)	8 (19.5)	0.139
Epigastric pain	33 (30.8)	18 (45)	0.108
Early satiety	13 (12.1)	7 (17.1)	0.433
Belching	0 (0)	1 (2.4)	0.105
Dysphagia	39 (36.4)	10 (24.4)	0.163
Odynophagia	11 (10.3)	2 (4.9)	0.299
Melena	9 (8.4)	4 (9.8)	0.796
Isolated IME and IME combinations with IMG and IMDC			
Isolated IME	34 (31.8)	7 (17.1)	0.074
Co-occurrence of IME and IMG	62 (57.9)	13 (31.7)	0.004
Co-occurrence of IME, IMG, and IMDC	6 (5.6)	17 (41.5)	<0.001
Treatment			
PPI administration[1], n = 88	24 (36.9)	8 (34.8)	0.854
PPI regimen modification[2], n = 50	14 (37.8)	3 (21.4)	0.267
Dose escalation	9 (25)	2 (14.3)	0.412
Class modification	7 (18.9)	1 (7.1)	0.302
H_2 blocker administration[1], n = 128	4 (4.3)	3 (8.3)	0.373
H_2 blocker regimen modification[2], n = 12	1 (12.5)	0 (0)	
Dose escalation	0 (0)	0 (0)	0.460
Class modification	1 (0)	0 (0)	0.460
Sucralfate administration	28 (26.7)	14 (34.1)	0.370
Intravenous steroids needed	0 (0)	9 (30)	<0.001
SIT3	0 (0)	17 (41.5)	<0.001
Time from IME onset to SIT use, *median (IQR), days*	-	18 (3.5-54.5)	
Multiple SIT agents used, n = 17	0 (0)	9 (52.9)	<0.001
Number of SIT doses, *median (IQR)*	0 (0)	2 (1-4)	
Outcomes			
Clinical improvement/remission	61 (59.8)	28 (71.8)	0.187
Duration of IME symptoms, *median (IQR), days*	45 (19.5-81.5)	12 (7.2-42)	0.015
Endoscopic remission, n = 37	13 (44.8)	6 (75)	0.131
Histological remission, n = 33	6 (25)	3 (33.3)	0.632
Hospitalization for IME	39 (36.4)	30 (73.2)	<0.001
Length of hospitalization, *median (IQR), days*	7 (3-10)	7 (3-10.5)	0.956
Multiple hospitalizations, n = 69	12 (30.7)	7 (23.3)	0.493
ICI held	45 (44.6)	29 (74.4)	0.002

(*Contd...*)

Table 4 (*Continued*)

Feature/outcome	No. (%)		
	No steroid treatment, n=107	Steroid treatment, n=41	P-value
ICI resumed, n = 74	16 (36.4)	6 (20.7)	0.153
IME recurrence within 6 months of the index event	5 (5.3)	5 (14.3)	0.087
All-cause mortality	52 (48.6)	15 (36.6)	0.189
Length of follow up[4], *median (IQR), years*	0.9 (0.3-2.1)	0.6 (0.3-2.3)	0.898

[1]Included patients without prior use of PPI or H_2 blocker
[2]Included patients who had used PPIs prior to the onset of IME
[3]SITs used to treat colitis include infliximab, vedolizumab and ustekinumab
[4]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death
CTCAE, common terminology criteria for adverse events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; IMDC, immune-mediated diarrhea and colitis; IME, immune checkpoint inhibitor-related esophagitis; IMG, immune-mediated gastroenteritis; IQR, interquartile range; PPI, proton pump inhibitor; SIT, selective immunosuppressive therapy

both chemotherapy [31] and immunotherapy [32,33]. In our cohort, PPI use in isolated IME offered no significant clinical benefit, contrasting with earlier findings [3]. Therefore, PPIs are recommended for severe esophagitis, prior bleeding, Barrett's esophagus [26] or mucosa prone to ulceration, where their benefits are more likely to be observed.

IME management currently depends on disease severity and clinician expertise. For CTCAE grade ≥2, the standard approach involves withholding ICI and administering acid-reducing agents, particularly PPIs, used in 33% of oncology patients with upper GI symptoms [34]. Corticosteroids, typically prednisone, are reserved for moderate to severe presentations [35-39] and are tapered once symptoms regress to grade 1. Polymeric sucralfate, a mucosal barrier therapy, offers a cytoprotective alternative that promotes ulcer healing and sustains remission longer than antisecretory agents [40]. It shields the healing process from acidity [40] and enhances the activity of growth factors—particularly fibroblast growth factor, vital for angiogenesis and epithelial repair [41]. It has shown efficacy against radiation-induced esophagitis [42] and chemotherapy-related mucositis [43], with minimal systemic absorption (5%) [41]. Although our sample size was insufficient to assess sucralfate specifically for IME, existing evidence supports its potential as an alternative. However, additional studies are needed to better assess the management of IME in this context.

This study identified that corticosteroids were less frequently prescribed for IME, unless accompanied by IMG/IMDC or severe enough to warrant hospitalization or ICI discontinuation. However, corticosteroid use was associated with faster symptom improvement, and a similar trend was seen for isolated IME, which aligns with the immune-mediated nature of irAEs. Emerging steroid treatments, such as budesonide—a gut-selective anti-inflammatory—offer an alternative to conventional immunosuppressive therapies. Budesonide, with low systemic absorption due to hepatic first-pass metabolism, offers an efficacy comparable to prednisone [44] while minimizing interference with immunotherapy outcomes [45,46], infection risk [47] and metabolic side effects, such as hyperglycemia, osteoporosis and GI ulcers. An open-capsule approach is under evaluation, with early results showing a rapid clinical response and 58% achieving sustained corticosteroid-free remission for IMG [48]. Budesonide oral suspension, effective in eosinophilic esophagitis, showed a 56% histologic response vs. 10% with placebo [49]. Both approaches offer promising alternatives for the management of IME, providing localized therapy without systemic adverse effects associated with traditional corticosteroids. Further testing is needed to assess budesonide's bioavailability along the esophagus and whether it has similar efficacy for IMG.

This study had several limitations. First, its retrospective design limited data to chart documentation, making it difficult to capture variables (e.g., PPI start/end date, dosage, and class). Second, underlying conditions prompting PPI use were not reported and may have influenced outcomes. Third, reliance on EGD for diagnosing ICI-associated upper GI toxicity may have missed cases, especially if performed elsewhere or not at all. For the 9 patients receiving both ICI and chemotherapy with chemically reactive changes, the contribution of ICI alone is unclear. Fourth, rare cases of delayed radiation esophagitis may have been included because of subtle or absent objective findings. Fifth, nonspecific symptoms such as nausea and vomiting, which affect up to 70% of cancer patients [50], prevented a broad screening of all patients receiving ICIs. Only symptomatic patients who underwent EGD were included, limiting the generalizability of the 5.6% IME incidence. Finally, while we suggest that PPIs offer limited benefit, and corticosteroids present a potential alternative, this remains speculative in the absence of clinical trials controlling for potential confounders.

To conclude, this study offers the most comprehensive analysis of IME to date, with the largest sample size reported. Our findings show an increased incidence of IME of 5.6%, probably reflecting the expanded use of ICIs, with anti-PD-1/PD-L1 therapies being the primary culprits. While PPIs demonstrated no significant clinical benefit, corticosteroids were associated with faster symptom resolution, aligning with other irAE

management. Given the growing use of ICIs, these findings contribute to our understanding of effective management strategies for this irAE. Further prospective studies are needed to validate these results, assess alternative treatments, such as budesonide, and define optimal corticosteroid regimens.

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Summary Box

What is already known:

- Immune checkpoint inhibitor-related esophagitis (IME) is a rare immune-related adverse event associated with immune checkpoint inhibitor (ICI) therapy, but only limited data are available apart from case reports and small series
- IME typically presents within 4 months of ICI initiation, with upper gastrointestinal symptoms such as nausea, vomiting and dysphagia
- Current management of IME is not standardized and often relied on clinicians' discretion, with proton pump inhibitors (PPIs) and corticosteroids used variably
- Corticosteroids are standard for moderate to severe irAEs, but their role in isolated IME remains unclear

What the new findings are:

- This study reports the largest IME cohort to date, identifying a higher IME incidence (5.6%) than previously reported 3%, probably due to expanded ICI use
- Corticosteroids were associated with significantly faster symptom resolution, supporting their use in IME management, including in isolated cases
- PPI use offered no significant clinical benefit in isolated IME, and may not be necessary except in select high-risk scenarios
- Prior radiotherapy was significantly associated with isolated IME, suggesting a potential synergistic effect with ICIs in esophageal mucosa injury

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Supplementary material

Supplementary Table 1 Endoscopic and histopathological features of immune checkpoint inhibitor-related esophagitis, n=148

Features	No. (%)
Endoscopic features	
Normal	44 (29.7)
Non-ulcerative inflammation	81 (54.7)
Ulcerative inflammation	21 (14.2)
Spontaneous bleeding	1 (0.7)
Location of esophageal inflammation	
Upper third	31 (20.9)
Middle third	32 (21.6)
Lower third	83 (56.1)
Time from IME onset to upper endoscopy, *median (IQR), days*	3 (0-20)
Histological features	
Normal	3 (2)
Acute inflammation	42 (28.4)
Chronic inflammation	18 (12.2)
Chemical reactive changes	33 (22.3)
Chronic inactive inflammation	9 (6.1)
Co-occurrence of infections[1]	9 (6.1)

[1]Included 5 cases of candidiasis, 2 cases of HSV and 1 case of *H. pylori*

IME, immune checkpoint inhibitor-related esophagitis; IQR, interquartile range

Supplementary Table 2 Clinical features and outcomes among patients with isolated immune checkpoint inhibitor-related esophagitis treated with proton pump inhibitors vs. those not treated with proton pump inhibitors, n=41

Features	No. (%)		
	No PPI treatment, n=31	PPI treatment, n=10	P-value
Time from ICI to IME, *median (IQR), months*	3.5 (0.9-10.1)	5.1 (3.1-15.2)	0.564
Length of ICI, *median (IQR), months*	8.4 (2.6-12)	13.7 (2.3-23.8)	0.524
CTCAE grade for esophagitis			0.307
0-1	3 (9.7)	0 (0)	
2 and above	28 (90.3)	10 (100)	
Presenting symptoms			
Nausea	18 (58.1)	4 (40)	0.319
Emesis	6 (19.4)	1 (10)	0.494
Acid reflux	17 (54.8)	5 (50)	0.790
Epigastric pain	9 (29)	2 (20)	0.575
Early satiety	5 (16.1)	1 (10)	0.633
Belching	1 (3.2)	0 (0)	0.565
Dysphagia	14 (45.2)	5 (50)	0.790
Odynophagia	5 (16.1)	3 (30)	0.336
Melena	2 (6.5)	2 (20)	0.209
Treatment			
H_2 blocker administration1, n=35	1 (3.7)	1 (12.5)	0.346
H_2 blocker regimen modification2, n=5	1 (33.3)	0 (0)	0.361
Dose escalation	0 (0)	0 (0)	-
Class modification	1 (33.3)	0 (0)	0.361
Sucralfate administration	7 (22.6)	4 (40)	0.280
Steroid administration	5 (16.1)	2 (20)	0.777
Time from IME onset to steroid use, *median (IQR), days*	22 (3-31.5)	1 (1-1)	0.245
Duration of steroid treatment, median (IQR), *days*	39 (15.5-84.5)	78.5 (40-78.5)	0.245
Intravenous steroids needed	1 (9.1)	0 (0)	0.486
SIT[3]	0 (0)	1 (10)	0.079
Time from IME onset to SIT use, *median (IQR), days*	-	26 (26-26)	-
Number of SIT doses, *median (IQR)*	-	1 (1-1)	-
Outcomes			
Clinical improvement/remission	16 (57.1)	7 (70)	0.475
Duration of IME symptoms, median (IQR), days	30 (21-65.5)	54 (2-224)	0.781
Endoscopic improvement/remission, n=13	7 (70)	2 (66.7)	0.913
Histological improvement/remission, n=7	3 (50)	0 (0)	0.350
Hospitalization for IME	11 (35.5)	5 (50)	0.413
Length of hospitalization, median (IQR), days	6 (5-10)	7 (2.5-14.5)	0.864
Multiple hospitalizations, n=16	4 (36.4)	0 (0)	0.119
ICI held	19 (65.5)	4 (50)	0.423
ICI resumed, n=23	9 (47.4)	2 (50)	0.924
IME recurrence within 6 months of the index event	2 (7.4)	0 (0)	0.401
All-cause mortality	15 (48.4)	6 (60)	0.523
Length of follow up[4], *median (IQR), years*	0.6 (0.3-1.5)	1.4 (0.2-2.4)	0.404

Patients were included in the PPI treatment group only if they had not received a PPI within 3 months prior to the onset of ICI therapy and up to the onset of IME, or if, after IME onset, the PPI dose was escalated or the class was switched to a more potent formulation. This ensured that the PPI was used as a treatment for the condition

[1]Included patients without prior use of PPI or H_2 blocker

[2]Included patients who had used PPIs prior to the onset of IME

[3]SITs used to treat colitis include infliximab, vedolizumab and ustekinumab

[4]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death

CTCAE, Common Terminology Criteria for Adverse Events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; IMC, immune-mediated diarrhea and colitis; IME, immune checkpoint inhibitor-related esophagitis; IMG, immune-mediated gastroenteritis; IQR, interquartile range; PPI, proton pump inhibitor; SIT, selective immunosuppressive therapy

Supplementary Table 3 Clinical features and outcomes among patients with isolated immune checkpoint inhibitor-related esophagitis treated with H_2 blockers vs. those not treated with H_2 blockers, n=41

Feature/outcome	No. (%)		
	No H_2 blocker treatment, n=38	H_2 blocker treatment, n=3	P-value
Time from ICI to IME, *median (IQR), months*	8.7 (2.5-16.5)	5.1 (0.8-50.5)	0.689
Length of ICI, *median (IQR), months*	3.7 (1.4-10.6)	2.9 (1.4-44.8)	0.764
CTCAE grade for esophagitis			0.613
0-1	3 (100)	0 (0)	
2 and above	35 (92.1)	3 (7.9)	
Presenting symptoms			
Nausea	20 (90.9)	2 (9.1)	0.639
Emesis	5 (71.4)	2 (28.6)	0.018
Acid reflux	21 (95.5)	1 (4.5)	0.463
Epigastric pain	11 (100)	0 (0)	0.276
Early satiety	5 (83.3)	1 (16.7)	0.341
Belching	3 (75)	1 (25)	0.153
Dysphagia	17 (89.5)	2 (10.5)	0.463
Odynophagia	7 (87.5)	1 (12.5)	0.530
Melena	4 (100)	0 (0)	0.554
Treatment			
PPI administration[1], n=22	5 (83.3)	1 (16.7)	0.449
PPI regimen modification[2], n=16	4 (100)	0 (0)	0.551
Dose escalation	7 (100)	0 (0)	0.385
Class modification	2 (66.7)	1 (33.3)	0.263
Sucralfate administration	9 (81.8)	2 (18.2)	0.106
Steroid administration	7 (100)	0 (0)	0.414
Intravenous steroids needed	1 (100)	0 (0)	0.790
Outcomes			
Clinical improvement/remission	22 (95.7)	1 (4.3)	0.315
Duration of IME symptoms, median (IQR), days	30 (21-71)	81 (81-81)	0.340
Hospitalization for IME	15 (93.8)	1 (6.3)	0.834
Length of hospitalization, median (IQR), days	6 (4-10)	7 (7-7)	0.913
Multiple hospitalizations, n=16	4 (100)	0 (0)	0.551
ICI held	21 (91.3)	2 (8.7)	0.867
ICI resumed, n=23	11 (100)	0 (0)	0.156
IME recurrence within 6 months of the index event	2 (100)	0 (0)	0.806
All-cause mortality	18 (85.7)	3 (14.3)	0.079
Length of follow up[3], *median (IQR), years*	0.9 (0.3-2.0)	0.3 (0.2-0.6)	0.293

[1]Included patients without prior use of PPI or H_2 blocker
[2]Included patients who had used PPIs prior to the onset of IME
[3]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death
CTCAE, Common Terminology Criteria for Adverse Events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; IMC, immune-mediated diarrhea and colitis; IME, immune checkpoint inhibitor-related esophagitis; IMG, immune-mediated gastroenteritis; IQR, interquartile range; PPI, proton pump inhibitor; SIT, selective immunosuppressive therapy

Supplementary Table 4 Clinical features and outcomes among patients with isolated immune checkpoint inhibitor-related esophagitis treated with steroids vs. those not treated with steroids, n=41

Features	No. (%)		
	No steroid treatment, n=34	Steroid treatment, n=7	P-value
Time from ICI to IME, *median (IQR), months*	5.1 (1.4-12.3)	3.3 (0.9-3.8)	0.406
Length of ICI, *median (IQR), months*	9 (3.7-18.1)	2.6 (1.9-4.8)	0.061
CTCAE grade for esophagitis			0.414
0-1	3 (100)	0 (0)	
2 and above	31 (81.6)	7 (18.4)	
Presenting symptoms			
Nausea	17 (50)	5 (71.4)	0.301
Emesis	5 (14.7)	2 (28.6)	0.375
Acid reflux	18 (52.9)	4 (57.1)	0.839
Epigastric pain	9 (26.5)	2 (28.6)	0.909
Early satiety	4 (11.8)	2 (28.6)	0.252
Belching	0 (0)	1 (14.3)	0.026
Dysphagia	14 (41.2)	5 (71.4)	0.144
Odynophagia	7 (20.6)	1 (14.3)	0.702
Melena	2 (5.9)	2 (28.6)	0.065
Treatment			
PPI administration[1], n=22	5 (25)	1 (50)	0.449
PPI regimen modification[2], n=16	3 (25)	1 (25)	>0.99
Dose escalation	2 (18.2)	1 (25)	0.770
Class modification	1 (8.3)	0 (0)	0.551
H_2 blocker administration[1], n=35	2 (6.7)	0 (0)	0.552
H_2 blocker regimen modification[2], n=5	1 (1)	0 (0)	0.361
Dose escalation	3 (100)	2 (100)	-
Class modification	1 (33.3)	0 (0)	0.361
Sucralfate administration	8 (23.5)	3 (42.9)	0.293
Time from IME onset to steroid use, *median (IQR), days*	-	21 (0-29)	-
Duration of steroid treatment, *median (IQR), days*	-	40 (28-94)	-
Intravenous steroids needed	0 (0)	1 (20)	0.126
SIT[3]	0 (0)	1 (14.3)	0.028
Time from IME onset to SIT use, *median (IQR), days*	-	26 (26-26)	-
Number of SIT doses, median (IQR)	-	1 (1-1)	-
Outcomes			
Clinical improvement/remission	19 (59.4)	4 (66.7)	0.737
Duration of IME symptoms, median (IQR), days	46.5 (25.5-78.5)	9 (2.5-71)	0.130
Endoscopic improvement/remission, n=13	7 (63.6)	2 (100)	0.305
Histological improvement/remission, n=7	2 (40)	1 (50)	0.809
Hospitalization for IME	11 (32.4)	5 (71.4)	0.054
Length of hospitalization, median (IQR), days	7 (5-10)	3 (1.5-10.5)	0.231
Multiple hospitalizations, n=16	3 (27.3)	1 (20)	0.755
ICI held	16 (53.3)	7 (100)	0.022
ICI resumed, n=23	9 (56.3)	2 (28.6)	0.221
IME recurrence within 6 months of the index event	1 (3.2)	1 (20)	0.129
All-cause mortality	17 (50)	4 (57.1)	0.731
Length of follow up[4], *median (IQR), years*	0.7 (0.3-2.0)	0.6 (0.3-1.5)	0.917

[1]Included patients without prior use of PPI or H_2 blocker
[2]Included patients who had used PPIs prior to the onset of IME
[3]SITs used to treat colitis include infliximab, vedolizumab and ustekinumab
[4]From the onset of immune checkpoint inhibitor-related esophagitis to the most recent follow up or date of death
ICI, immune checkpoint inhibitor; IME, immune checkpoint inhibitor-related esophagitis; IQR, interquartile range; CTCAE, Common Terminology Criteria for Adverse Events; IMG, immune-mediated gastroenteritis; IMC, immune-mediated diarrhea and colitis; PPI, proton pump inhibitor; H_2 blocker, histamine 2 receptor blocker; SIT, selective immunosuppressive therapy

Supplementary Table 5 Univariate analysis of factors associated with clinical improvement and/or remission among patients with isolated immune checkpoint inhibitor-related esophagitis, n=41

Factors	Odds ratio (95% confidence interval)	P-value
CTCAE grade	0.7 (0.06-9.0)	0.821
Age	0.9 (0.9-1.06)	0.266
PPI treatment vs. no PPI	1.7 (0.3-8.2)	0.478
H_2 blocker treatment vs. no H_2 blocker	0.3 (0.02-3.5)	0.338
Sucralfate treatment vs. no sucralfate	0.5 (0.1-2.3)	0.430
Steroid treatment vs. no steroid	1.3 (0.2-8.6)	0.738
ICI maintained vs. discontinuation	0.6 (0.1-2.5)	0.494

CTCAE, common terminology criteria for adverse events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor

Supplementary Table 6 Multivariate analysis of factors associated with clinical improvement and/or remission among patients with isolated immune checkpoint inhibitor-related esophagitis, n=41

Factors	Odds ratio (95% confidence interval)	P-value
CTCAE grade	0.6 (0.04-9.7)	0.756
Age	0.9 (0.9-1.02)	0.216
PPI treatment vs. no PPI	3.2 (0.4-24.2)	0.251
H_2 blocker treatment vs. no H_2 blocker	0.5 (0.03-9.5)	0.687
Sucralfate treatment vs. no sucralfate	0.4 (0.07-2.5)	0.356
Steroid treatment vs. no steroid	1.7 (0.2-14.2)	0.609
ICI maintained vs. discontinuation	0.6 (0.1-3.7)	0.641

CTCAE, Common terminology criteria for adverse events; H_2 blocker, histamine 2 receptor blocker; ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor