



Risk factors of perforation in gastric stromal tumors during endoscopic resection: a retrospective case–control study

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Abstract

Background and aims Perforation is a common complication during endoscopic resection (ER) of gastric gastrointestinal stromal tumors (gGISTs) associated with secondary infections, sepsis, hospitalization time and cost. However, the risk factors of perforation remain controversial. This study aimed to investigate the risk factors for perforation during ER of gGISTs.

Methods This retrospective case–control study included consecutive patients with gGISTs who underwent ER between June 2009 and November 2021 at the Nanjing Drum Tower Hospital. Univariate and multivariate analyses were performed to investigate the risk factors for perforation. Sensitivity analyses with propensity scoring (PS) were performed to evaluate the stability of the independent effects.

Results In total, 422 patients with gGISTs were included. The following factors were associated with perforation during ER: in the non-intraluminal growth patterns (all confounders adjusted odds ratio [aOR]: 5.39, 95% CI 2.99–9.72, $P < 0.001$), in the gastric fundus (aOR 2.25, 95% CI 1.40–3.60, $P = 0.007$), sized ≥ 2 cm (aOR 1.70, 95% CI 1.04–2.77, $P = 0.035$), in the lesser curvature (aOR 0.12, 95% CI 0.05–0.27, $P < 0.001$), and in the gastric cardia (aOR 0.13, 95% CI 0.04–0.50, $P = 0.003$). The PS analysis confirmed the stable independent effects of these identified risk factors.

Conclusions ERs of gGISTs in non-intraluminal growth patterns, in the gastric fundus, and with larger tumor size were independent risk factors for perforation. While tumors in the lesser curvature or gastric cardia were independent protective factor for perforation.

Keywords Gastrointestinal stromal tumors · Endoscopic resection · Perforation · Risk factors · Case–control study

Abbreviations

CI Confidence interval
EFTR Endoscopic full–thickness resection
ER Endoscopic resection

ESD Endoscopic submucosal dissection
EU Endoscopic ultrasound
GIST Gastrointestinal stromal tumor
IPTW Inverse probability of treatment weighting
MP Muscularis propria
NIH National Institutes of Health
PS Propensity score
PSM Propensity score matching
SMTs Submucosal tumors

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Introduction

Gastrointestinal stromal tumor (GIST) is the most prevalent type of mesenchymal tumors of the digestive tract, with 60–70% occurring in the stomach [1]. The annual incidence of malignant GISTs is relatively low (10 cases per million), but asymptomatic small GISTs (< 20 mm) can be detected in approximately 35% of patient autopsies [2]. Although the

use of tyrosine kinase inhibitors has significantly improved the prognosis of gastric GISTs (gGISTs), surgical resection remains the main therapeutic choice [3, 4]. Endoscopic resection (ER) has recently been adopted as an alternative modality to laparoscopic wedge excision for removing small gGISTs (< 35 mm), because it is less invasive and has comparable recurrence, disease-free survival, and complication rates [5–10]. Moreover, ER has been recommended as an alternative to surveillance for treating gGISTs smaller than 20 mm [11].

Although tremendous progress has been made in endoscopic techniques, tumor recurrence and perforation remain as pivotal disadvantages. To reduce tumor recurrence, multiple new endoscopic techniques have been reported to achieve *en bloc* resection, and several stratification systems have been established to predict R1 resection for additional surgery [12–14]. Perforation is not rare in gGISTs who undergo ER (rates ranged from 6.7 to 62.5%), although most can be managed with endoscopic intervention or conservative therapy [7, 8, 15–18]. However, endoscopic perforation is closely related to secondary infections and sepsis, and was associated with longer hospitalization time and higher hospitalization cost [7, 8]. Therefore, it is crucial to identify the risk factors for perforation of gGISTs during ER.

A large lesion size and extraluminal growth are independent risk factors for perforation in patients with GISTs who underwent ER [19, 20]. Although gGISTs were included in these studies, the lack of confounders associated with the stomach, such as anatomical and circumferential locations of the tumor, limited the generalizability of the conclusions. Several studies found that lesions in the fundus had a higher perforation rate than those in other locations, but other studies found no significant difference in perforation rate between tumor locations [12, 21, 22]. In addition, the independent association between tumor location and perforation incidence has not been investigated.

This study aimed to investigate the independent risk factors associated with perforation in gGISTs treated with ER. Subgroup and multiple sensitivity analyses were performed to validate independent effects.

Methods

Study design and participants

This retrospective case–control study was conducted at the Nanjing Drum Tower Hospital (NDTH) and was approved by the Medical Ethics Committee of NDTH (approval no. 2022–110-01). The inclusion criteria were consecutive patients who underwent ER and were diagnosed with gGISTs by pathological and immunohistochemical examination between June 2009 and November 2021 in the NDTH.

GISTs were diagnosed based on the immunohistochemical reactions of CD117, DOG-1 and CD34 [23]. The exclusion criteria were as follows: (1) patients with multiple synchronous gGISTs, gastric intraepithelial neoplasia or carcinomas; (2) patients with a history of subtotal gastrectomy; (3) patients who underwent incomplete resection; and (4) patients who underwent ER with intentional perforation. Intentional perforation was conducted by cap-assisted endoscopic full-thickness resection (EFR-C) according to Yang et al. [24], which was selectively carried out from May 2012 and indicated for gGISTs smaller than 1.5 cm, accounting for 29.3% (92/314) of all ≤ 1.5 cm cases.

ER procedures

ER was performed under sedation with intravenous propofol (1.5–2.5 mg/kg for induction and 4–12 mg/kg/h for maintenance) and midazolam (0.05 mg/kg) or general anesthesia with endotracheal intubation in the left decubitus position. All procedures were performed by 14 qualified endoscopists (Supplementary Table 1) using a single-channel endoscope (Q-260 J; Olympus) with a transparent cap (ND-201–11,802; Olympus). Endoscopic submucosal dissection (ESD) was attempted first in all cases according to Xin-gang Shi et al. [25] (Fig. 1a): (1) Marking around the tumor with an argon plasma coagulation (APC)/dual knife (KD-650L, Olympus); (2) A mixture of 0.9% saline solution containing epinephrine (1:10,000) and indigo carmine dye was repeatedly injected around the lesion using a single use injector (NM-4L-1; Olympus); (3) The submucosal layer was dissected until the tumor was exposed, and the tumor was excavated from the submucosa and then gradually dissected from the muscularis propria (MP) using a high-frequency electronic cutting device (Vio 300D, Erbe, Tübingen, Germany), a dual knife, or an insulated-tip knife (KD-611 L, IT2, Olympus) until the tumor was completely removed while keeping the MP layer intact. For tumors with close connection to the serosal layer, Endoscopic subserosal dissection (ESSD) was attempted first during separation of the tumor from the serosal layer as we previously reported [26] (Fig. 1 b, Video 1): a subserosal injection is used to separate the tumor from the outer omentum layer while maintaining serosal layer integrity. The tumor is then gradually separated within the subserosal space, with the serosal layer remaining intact, eventually achieving complete resection. However, if ESD and ESSD fail to achieve complete resection while keeping the MP layer or serosal layer intact, Endoscopic Full-Thickness Resection (EFTR) is performed as a priority to ensure complete resection according to previous reports [13, 27] (Fig. 1c). EFTR involves a full-thickness resection of both the tumor and the surrounding stomach wall, including the entire MP and serosal layer. After EFTR, the gastric cavity is directly connected to the abdominal cavity, resulting in

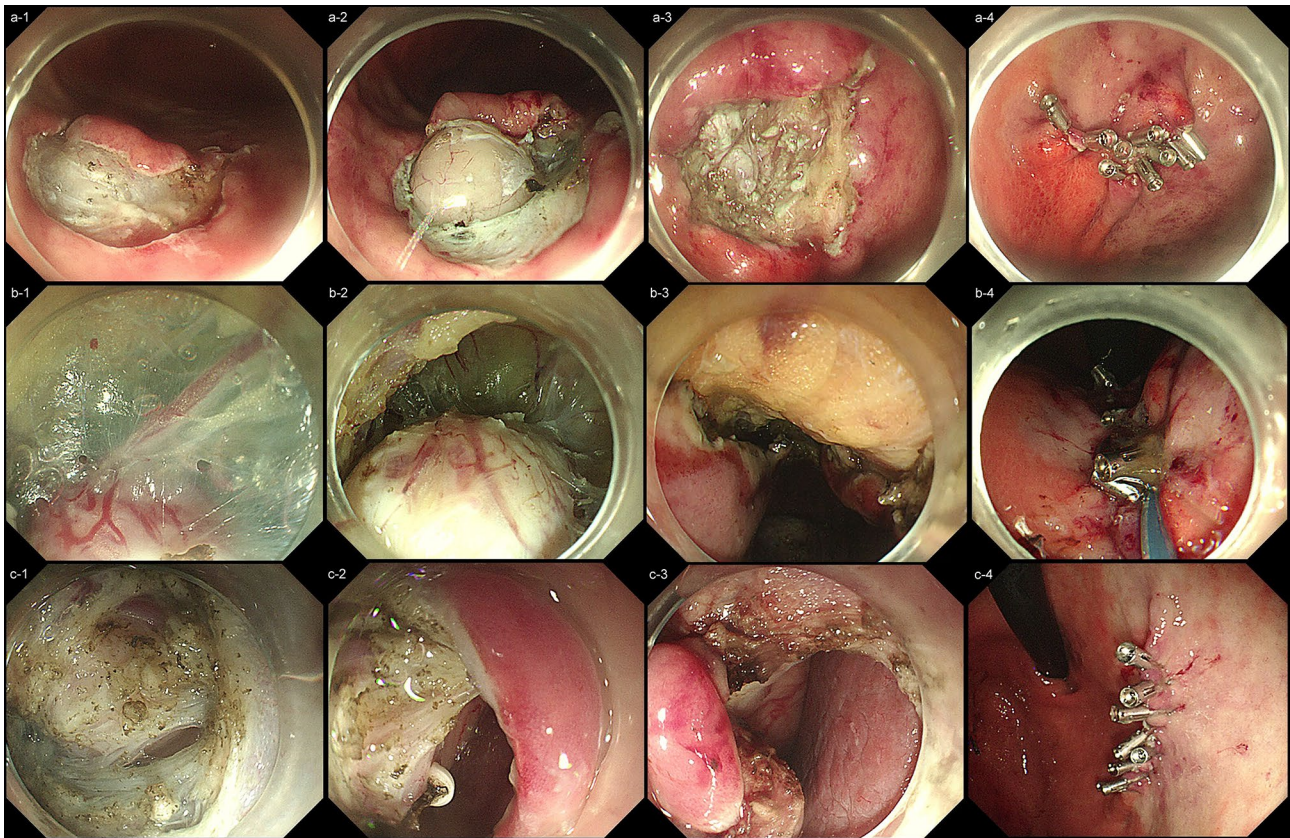


Fig. 1 Endoscopic resection methods for gastric gastrointestinal stromal tumors. **a** Endoscopic submucosal dissection (ESD): **a-1** Marking, submucosa injection and circumferential incision; **a-2** Expose the tumor, excavate and dissect from the muscularis propria; **a-3** Remove the tumor with the muscularis propria layer intact; **a-4** Closure of the incision; **b**: Endoscopic subserosal dissection (ESSD): **b-1** Subserosal

injection; **b-2** Excavate the tumor with serosal layer intact; **b-3** Complete serosal layer after dissection with good gas storage capacity of the stomach; **b-4** Closure of the incision; **c** Endoscopic full-thickness resection (EFTR): **c-1** Tumor with extensive connection with serosal layer; **c-2** Full-thickness resection for complete resection; **c-3** Full-thickness perforation after resection; **c-4**: Closure of the incision

perforation in all cases. After dissection, the incision was closed using hemostatic clips (HX-610–90, HX-600–135, Olympus; ROCC-D-26–195-C, micro-tech, Nanjing, China).

Variables and outcomes

The primary outcome was perforation. Perforation was defined as direct endoscopic visualization of extra-gastric structures through an incomplete serosal layer (Intraoperative perforation) or radiographic evidence of pneumoperitoneum, and delayed perforation was defined as radiographic proved pneumoperitoneum without obvious intraoperative perforation [7]. *En bloc* resection was defined as the resection of a lesion with an intact capsule retrieved from the oral cavity. Complete resection was defined as tumors removed *en bloc*, with histopathological residual-negative margin (R0) [28]. The location of the gGIST lesion was classified into four circumferential locations (lesser curvature, anterior wall, greater curvature, and posterior wall) and five anatomical locations (cardia, fundus, body, angle, and antrum)

[29, 30]. The tumor size was measured by assessment of the postoperative resected specimen *in vitro*. The tumor growth pattern was estimated mainly using CT images, whereas small gGISTs undetected on CT were estimated using endoscopic ultrasound [31]. If over 90% of the tumor body was bulging inside or outside the gastric luminal space, it was defined as either an intra- or extraluminal type respectively, whereas if 50–90% of the tumor body was bulging inside or outside the gastric luminal space it was defined as either an intra- or extraluminal-dominant type respectively (Fig. 2) [19]. Malignancy potential was classified according to the modified National Institutes of Health (NIH) classification system of 2008 [32]. The operators were classified into two groups according to their experience in ER of upper digestive tumors (< or \geq 2000 cases). The learning curve effect was evaluated by dividing the first half of the ER procedures by the second half of each operator [33]. Adverse events were classified according to the Clavien–Dindo Grade [34]. Recurrence was defined as the detection of tumor by upper endoscopy or abdominal CT scan during follow-up in the

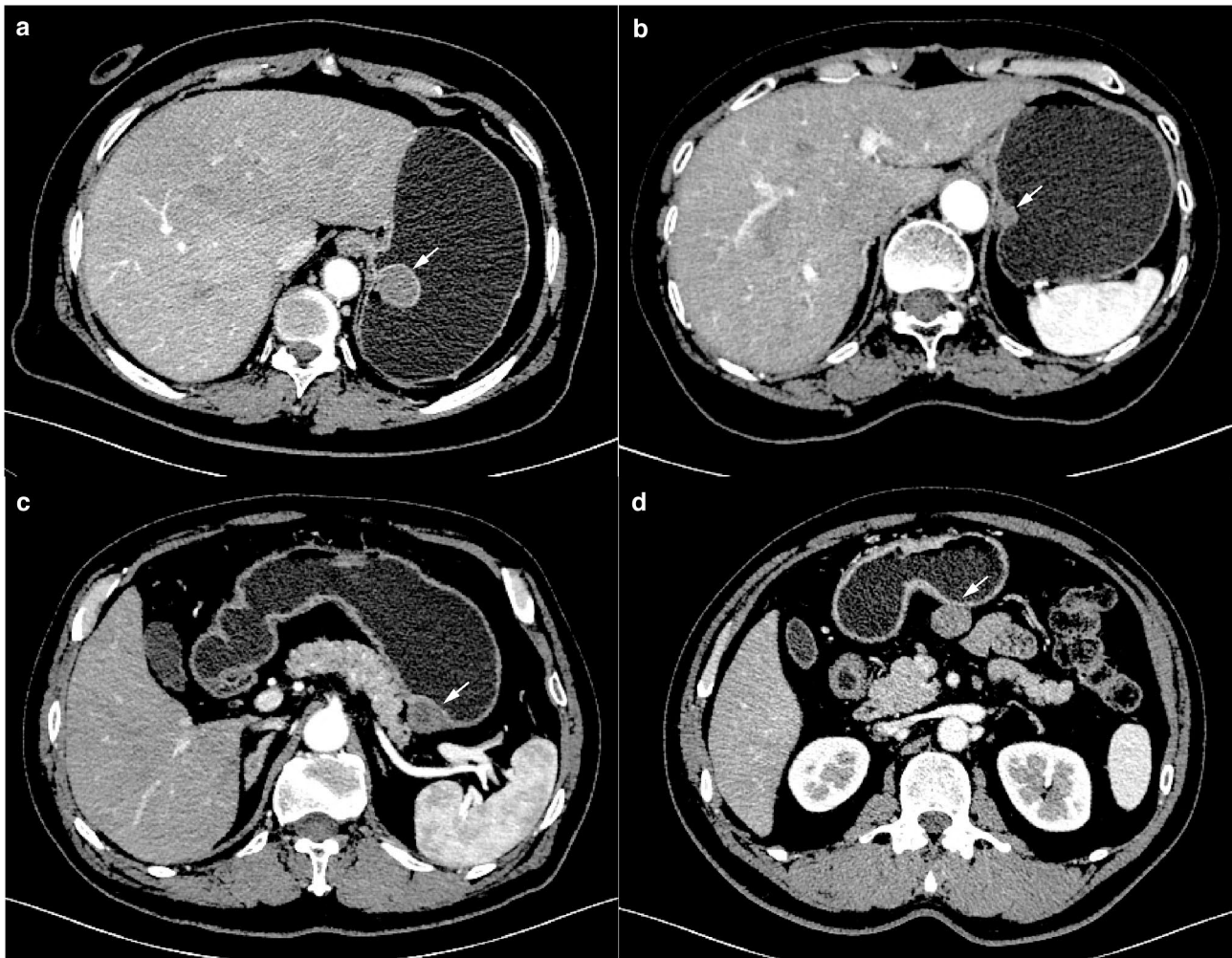


Fig. 2 Computed tomography (CT) evaluation of gastric gastrointestinal stromal tumor (gGIST) growth pattern (white arrow). **a** Intraluminal growth: CT showed a gGIST with over 90% of tumor bulging into the intraluminal space; **b** Intraluminal-dominant growth: CT showed

a gGIST with 2/3 of tumor bulging into the intraluminal space; **c** Extraluminal-dominant growth: CT showed a gGIST with 2/3 of tumor bulging into the extraluminal space; **d** Extraluminal growth: CT showed a gGIST mainly bulging into the extraluminal space

primary resection site (local) or distance [7]. Follow-up was performed 6 months after ER operation to evaluate local recurrence by upper endoscopy and annually thereafter by a surveillance endoscopy and abdominal CT scan [35]. The last observation was in 21 May 2022.

Statistical analysis

Data were categorized and described as frequencies (%) and compared between groups using the chi-squared test or Fisher's exact test. Univariate logistic regression was performed to investigate the effect size of the potential risk factors for perforation, and results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Based on the univariate analysis, we combined groups with similar effect values when performing multivariate analyses. Significant risk factors ($p < 0.05$) in univariate analysis

(anatomical location, circumferential location, growth pattern, and tumor size) were entered into a multivariate logistic regression model. The independent effect of the risk factors was assessed using two multiple logistic regression models, adjusted for selected confounding variables. Confounders adjusted in Model I were selected based on their associations with the outcomes of a change in effect estimated around $> 10\%$ (data not shown). In Model II, all potential covariates were included in the adjustment. The propensity score (PS) was applied as a sensitivity analysis to account for selection bias and ensure the stability of the independent effect, including inverse probability of treatment weighting (IPTW), propensity-score matching (PSM), and adjustment for propensity score [36, 37]. In the IPTW analysis, each patient was weighted by inverse probability to calculate the stabilized IPTW weight from all confounders. PSM analysis was used to calculate the propensity scores for each patient

using a multivariable logistic regression model that included all potential covariates. The nearest-neighbor method was used to create a matched control group at a 1:1 ratio. Statistical significance was set at $P < 0.05$ (two-sided). All analyses were performed using EmpowerStats (<https://www.empowerstats.com>) and the R statistical software (version 4.1.2; R Project for Statistical Computing).

Results

Baseline and clinicopathological characteristics

In total, 422 patients with 422 lesions were included in the final analysis including 169 lesions with perforation (163 intraoperative perforation and 6 delayed perforation, shown in Supplementary Table 2) and 253 controls without perforation (Fig. 3). The baseline and clinicopathological characteristics are shown in Table 1 and the proportion of each single item is shown in Fig. 4. Among all patients, 42.2% were male and 53.3% were aged ≥ 60.0 years. No statistically significant differences were observed in age ($P = 0.413$) or sex ($P = 0.954$) between the cases and controls.

Compared with controls, fewer lesions in perforation group were located in the lesser curvature (5.3% vs. 24.1%, $P < 0.001$) and gastric cardia (1.8 vs. 9.1%, $P < 0.001$), whereas more lesions were located in the gastric fundus (60.4 vs. 41.9%, $P < 0.001$). More tumors in the perforation

group were > 2 cm in size (42.6 vs. 30.8%, $P = 0.013$). The vast majority of lesions without perforation had an intraluminal growth pattern (83.8%); the latter was less prevalent in perforated lesions (61.5%, $P < 0.001$). The risk categories of the modified NIH classification for the cases and controls were as follows: very low (56.2 vs. 66.4%), low (36.2 vs. 26.5%), intermediate (5.9 vs. 4.7%), and high (1.8 vs. 2.4%). The experience (≥ 2000 cases: 43.8 vs. 41.5%, $P = 0.642$) and learning curvature (Second 50%: 56.2% vs. 47.0%, $P = 0.065$) of the operators were comparable between cases and controls.

Comparison of clinical outcomes

The clinical outcomes of ER with and without perforation were compared and shown in Table 2. Compared with controls, cases with perforation during ER were associated with a higher rate of sepsis (OR 3.67, 95% CI 1.40–9.63), a longer time until start of oral intake (b: 0.62 (days), 95% CI 0.40–0.84), longer postoperative hospital stays (b 1.13 (days), 95% CI 0.54–1.72) and higher total cost (b: 255.84 (\$), 95% CI 114.20–397.48) in multivariate analysis after adjusting for all confounders including age, sex, anatomical location, circumferential location, tumor size, growth pattern, operator, and operator learning curve. During a follow-up with mean time of 4.3 years, patients underwent ER without perforation showed no recurrence. While among patients with perforation during a mean follow-up of 3.7 years, one

Fig. 3 Flow chart of study inclusions and exclusions

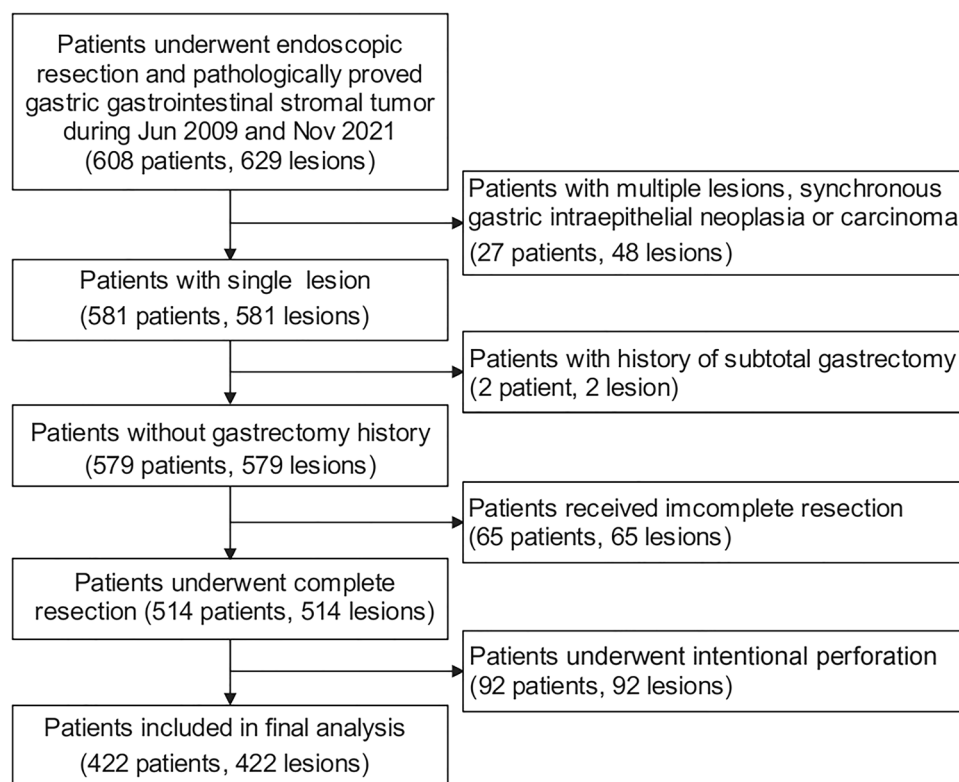


Table 1 Baseline characteristics of the participants

	Total <i>n</i> = 422	Perforation <i>n</i> = 169	No perforation <i>n</i> = 253	<i>P</i> value
Age(years), <i>n</i> (%)				0.413
< 60	197(46.7%)	83(49.1%)	114(45.1%)	
≥ 60	225(53.3%)	86(50.9%)	139(54.9%)	
Sex, <i>n</i> (%)				0.954
Male	178(42.2%)	71(42.0%)	107(42.3%)	
Female	244(57.8%)	98(58.0%)	146(57.7%)	
Circumferential location, <i>n</i> (%)				<0.001
Lesser curvature	70(16.6%)	9(5.3%)	61(24.1%)	
Anterior wall	98(23.2%)	48(28.4%)	50(19.8%)	
Greater curvature	164(38.9%)	81(47.9%)	83(32.8%)	
Posterior wall	90(21.3%)	31(18.3%)	59(23.3%)	
Anatomic location, <i>n</i> (%)				<0.001
Gastric body	151(35.8%)	50(29.6%)	101(39.9%)	
Gastric fundus	208(49.3%)	102(60.4%)	106(41.9%)	
Gastric cardia	26(6.2%)	3(1.8%)	23(9.1%)	
Gastric angle	8(1.9%)	2(1.2%)	6(2.4%)	
Gastric antrum	29(6.9%)	12(7.1%)	17(6.7%)	
Tumor size (cm), <i>n</i> (%) ^a				0.013
< 2	272 (64.5%)	97 (57.4%)	175 (69.2%)	
≥ 2	150 (35.5%)	72 (42.6%)	78 (30.8%)	
Tumor growth pattern, <i>n</i> (%) ^b				<0.001
Intraluminal	31(74.9%)	104(61.5%)	212(83.8%)	
Intraluminal-dominant	71(16.8%)	38(22.5%)	33(13.0%)	
Extraluminal-dominant	21(5.0%)	17(10.1%)	4(1.6%)	
Extraluminal	14(3.3%)	10(5.9%)	4(1.6%)	
Risk category of modified NIH classification, <i>n</i> (%)				0.157
Very-low risk	263(62.3%)	95(56.2%)	168(66.4%)	
Low risk	128(30.3%)	61(36.1%)	67(26.5%)	
Intermediate risk	22(5.2%)	10(5.9%)	12(4.7%)	
High risk	9(2.1%)	3(1.8%)	6(2.4%)	
Operator, <i>n</i> (%)				0.642
Experience < 2000	243(57.6%)	95(56.2%)	148(58.5%)	
Experience ≥ 2000	179(42.4%)	74(43.8%)	105(41.5%)	
The learning curve, <i>n</i> (%)				0.065
First 50%	208(49.3%)	74(43.8%)	134(53.0%)	
Second 50%	214(50.7%)	95(56.2%)	119(47.0%)	

NIH National Institutes of Health

^aMeasured by pathological assessment of postoperative resected specimen in vitro

^bMainly based on CT estimation (small GISTs that were unshown in CT were estimated by endoscopy ultrasound)

patient was detected recurrence in pancreas 6.4 years after first resection. The primary tumor size was 1.5 cm with a mitotic index of 4.5/50 HPF.

Risk factors for ER perforation

Then, a univariable logistic regression analysis was performed to evaluate the risk factors for perforation. The results showed that tumors in non-intraluminal growth

patterns (OR, 3.23; 95% CI, 2.05–5.10), located in the fundus (OR 2.11; 95% CI, 1.42–3.14), and sized ≥ 2 cm (OR 1.67; 95% CI 1.11–2.50) were associated with higher perforation risk. Tumors located in the lesser curvature (OR 0.18, 95% CI 0.09–0.37) or in cardia (OR 0.18, 95% CI 0.05–0.61) were associated with lower risk of perforation (Table 3).

The independent effect for each of these five factors remained significant when assessed by binary multivariable logistic regression analysis. Compared with cases

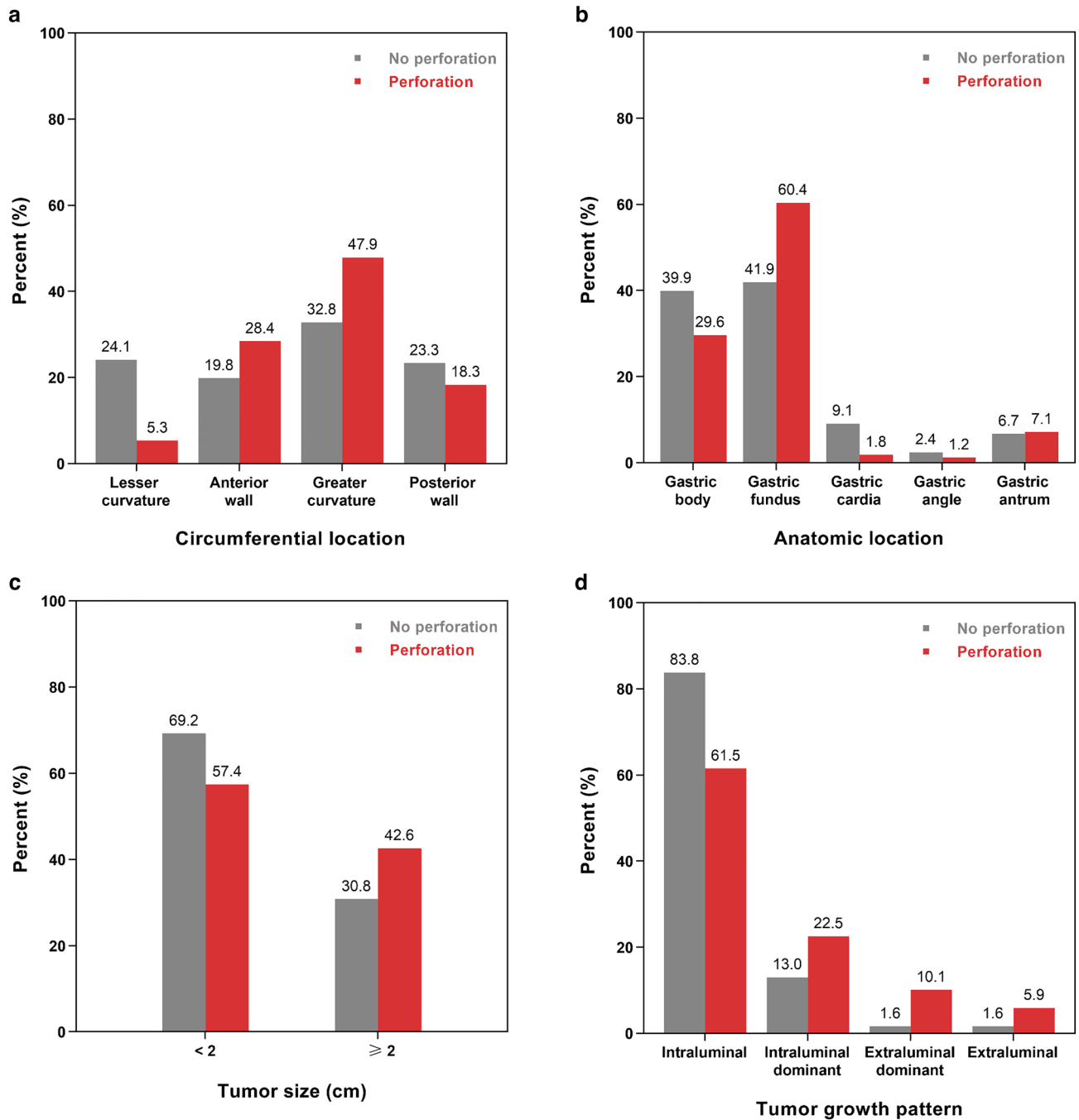


Fig. 4 Distribution of perforation stratified by: **a** Circumferential location; **b** Anatomic location; **c** Tumor size; **d** Growth pattern

located in lesser curvature, cases in anterior wall (OR 11.84; 95% CI 4.64–30.21), in greater curvature (OR 10.38; 95% CI 4.24–25.43), and in posterior wall (OR, 5.22; 95% CI, 2.03–13.46) were associated with a higher perforation risk. Compared with locating in gastric body, higher perforation risk was identified for locating in fundus (OR 1.78; 95% CI 1.07–2.94), and lower risk in cardia (OR, 0.21; 95% CI, 0.05–0.80). Tumor larger than 2 cm

was also associated with a higher perforation risk (OR 1.68, 95%CI 1.05–2.68). Moreover, compared with cases in intraluminal pattern, cases in intraluminal-dominant pattern (OR 4.21; 95% CI 2.19–8.09), in extraluminal-dominant pattern (OR 11.95; 95% CI 3.56–40.05), and in extraluminal pattern (OR 9.13; 95% CI 2.28–36.61) were all associated with higher perforation risk.

Table 2 Clinical outcomes of the patients grouped by perforation occurrence

	Statistics <i>n</i> (%)/mean ± s.d	Univariate analysis		Multivariate analysis ^a	
		OR/b (95% CI)	<i>P</i> value	OR/b (95% CI)	<i>P</i> value
Major bleeding (Clavien–Dindo Grade III)					
No perforation	1(0.4%)	Ref		Ref	
Perforation	2(1.1%)	2.82(0.25, 31.30)	0.570	None	
Sepsis (Clavien–Dindo Grade II)					
No perforation	9(3.7%)	Ref		Ref	
Perforation	23(13.1%)	3.96(1.78, 8.78)	<0.001	3.67(1.40, 9.63)	0.008
Time until start of oral intake (days)					
No perforation	1.8 ± 0.9	Ref		Ref	
Perforation	2.4 ± 1.2	0.66 (0.47, 0.86)	<0.001	0.62(0.40, 0.84)	<0.001
Postoperative hospital stays (days)					
No perforation	4.1 ± 1.4	Ref		Ref	
Perforation	5.3 ± 3.8	1.15(0.63, 1.67)	<0.001	1.13(0.54, 1.72)	<0.001
Total cost (\$)					
No perforation	2786.0 ± 582.9	Ref		Ref	
Perforation	3133.2 ± 804.2	347.19(214.87, 479.52)	<0.001	255.84 (114.20, 397.48)	<0.001
Follow-up(years)					
No perforation	4.3 ± 2.7				
Perforation	3.7 ± 2.3				
Recurrence					
No perforation	0	Ref		Ref	
Perforation	1	None		None	

^aAdjusted for all confounders (age, sex, anatomical location, circumferential location, tumor size, growth pattern, operator, learning curve)

Sensitivity analysis

Further sensitivity analyses were performed to evaluate the independent effects of these identified factors associated with perforation (Fig. 5). Baseline characteristics before and after IPTW/PSM were shown in Supplemental Table 3–12. Cases located in the lesser curvature were strongly associated with a lower risk of perforation in multiple models (Model I adjusted for growth pattern: OR 0.12; 95% CI 0.05–0.26; Model II adjusted for all: OR 0.12; 95% CI 0.05–0.27; IPTW: OR, 0.20; 95% CI 0.12–0.31; PSM: OR, 0.24; 95% CI 0.10–0.61; PS adjusted: OR, 0.17; 95% CI, 0.08–0.36). Cases located in the gastric cardia were also identified as a protective factor for perforation (Model I adjusted for circumferential location: OR 0.15; 95% CI, 0.04–0.52; Model II adjusted for all: OR 0.13; 95% CI, 0.04–0.50; IPTW: OR 0.27; 95% CI, 0.17–0.42; PSM: OR 0.35; 95% CI 0.08–1.56; PS adjusted: OR 0.18; 95% CI 0.05–0.60). Cases located in the gastric fundus were strongly associated with a higher risk of perforation (Model I adjusted for age, circumferential location, and growth pattern: OR 2.21; 95% CI 1.39–3.49; Model II adjusted for all: OR 2.25; 95% CI 1.40–3.60; IPTW: OR 1.96; 95% CI 1.32–2.92; PSM: OR 2.33; 95% CI 1.42–3.84; PS adjusted, OR 1.92, 95% CI 1.26–2.92). Meanwhile, lesions with a larger size (> 2 cm) were at a

higher risk of perforation (Model I adjusted for age, circumferential location, and growth pattern: OR, 1.82; 95% CI 1.14–2.90; Model II adjusted for all: OR 1.70; 95% CI 1.04–2.77; IPTW: OR 1.79; 95% CI 1.21–2.64; PSM: OR 1.54; 95% CI 0.91–2.60; PS adjusted: OR, 1.52; 95% CI, 0.98–2.34). Moreover, the presence of a non-intraluminal growth pattern was identified as a strong independent risk factor for perforation (Model I adjusted for anatomic and circumferential location: OR 6.06; 95% CI 3.40–10.81; Model II adjusted for all: OR 5.39; 95% CI 2.99–9.72; IPTW: OR 4.29; 95% CI 2.85–6.45; PSM: OR 5.23; 95% CI 2.81–9.73; PS adjusted: OR 3.82; 95% CI 2.33–6.25).

Discussion

In this retrospective case–control study, we evaluated the risk factors associated with perforation of gGISTs during ER. The results showed that cases in a non-intraluminal growth pattern (all confounders adjusted odds ratio [aOR], 5.39; 95% CI 2.99–9.72), located in the gastric fundus (aOR, 2.25; 95% CI 1.40–3.60), and sized ≥ 2 cm (aOR 1.70; 95% CI 1.04–2.77) were independent risk factors, while those located in the lesser curvature (aOR 0.12; 95% CI 0.05–0.27) or gastric cardia (aOR 0.13; 95% CI 0.04–0.50)

Table 3 Logistic-regression analysis for risk factors of perforation

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age (year)				
< 60	Ref		Ref	
≥ 60	0.85 (0.58, 1.26)	0.414	None	
Sex				
Male	Ref		Ref	
Female	1.01 (0.68, 1.50)	0.954	None	
Circumferential location				
Lesser curvature	Ref		Ref	
Anterior wall	6.51(2.91, 14.54)	<0.001	11.84(4.64, 30.21)	<0.001
Greater curvature	6.61(3.08, 14.20)	<0.001	10.38(4.24, 25.43)	<0.001
Posterior wall	3.56(1.56, 8.12)	0.003	5.22(2.03, 13.46)	0.001
Anatomic location				
Gastric body	Ref		Ref	
Gastric fundus	1.94(1.26, 3.00)	0.003	1.78(1.07, 2.94)	0.026
Gastric cardia	0.26(0.08, 0.92)	0.037	0.21(0.05, 0.80)	0.022
Gastric angle	0.67(0.13, 3.46)	0.636	1.02(0.14, 7.29)	0.987
Gastric antrum	1.43(0.63, 3.21)	0.392	0.69(0.26, 1.86)	0.464
Tumor size (cm)				
< 2	Ref		Ref	
≥ 2	1.67 (1.11, 2.50)	0.014	1.68 (1.05, 2.68)	0.030
Tumor growth pattern				
Intraluminal	Ref		Ref	
Intraluminal-dominant	2.35(1.39, 3.96)	0.001	4.21(2.19, 8.09)	<0.001
Extraluminal-dominant	8.66(2.84, 26.40)	<0.001	11.95(3.56, 40.05)	<0.001
Extraluminal	5.10(1.56, 16.64)	0.007	9.13(2.28, 36.61)	0.002
Operator				
Experience < 2000	Ref		Ref	
Experience ≥ 2000	1.10 (0.74, 1.63)	0.642	None	
Learning curve				
First 50%	Ref		Ref	
Second 50%	1.45 (0.98, 2.14)	0.065	None	

were protective factors for perforation. Multiple sensitivity analyses validated the stable effect value of these factors. To the best of our knowledge, our study included the largest sample size and number of variables to evaluate independent risk factors for perforation of gGISTs during ER. This study provides evidence for more precise endoscopic management strategies to minimize perforation of gGISTs under ER. Meanwhile, by identifying the cases with high risk of perforation, more aggressive interventions are optional including gastric lavage with a dilute antibiotic solution to reduce secondary infections and other related adverse events [38].

According to the latest consensus, endoscopic resection is suggested to be an optional therapeutic modality for small gGISTs, and the object of operation is to achieve R0 resection and avoid tumor rupture as far as possible, eventually ensuring a complete resection [4, 35, 39]. Tumor rupture and R1 resection were associate with higher risk

factor of peritoneal seeding, recurrence and a poor prognosis during resection of gastric GISTs [40, 41]. Therefore, achieving complete resection was the precondition of ER for gGISTs. For the patients received incomplete resection, the eventual perforation status of the additional treatment was unmeasurable. Because of the adverse events that may be caused by incomplete resection, optimizing the operation method and reducing perforation rate became nonsense in such cases. Meanwhile, multiple previous studies have reported relatively high complete resection rate ranging from 88 to 100% [9, 42–44]. Under our inclusive and exclusive criteria, the complete resection rate achieved 90.0% (422/469). The relatively high complete resection rate made us exclude the R1 resection cases to focus on the majority population and reduce the bias. Therefore, under such inclusion and exclusion criteria we believed that the

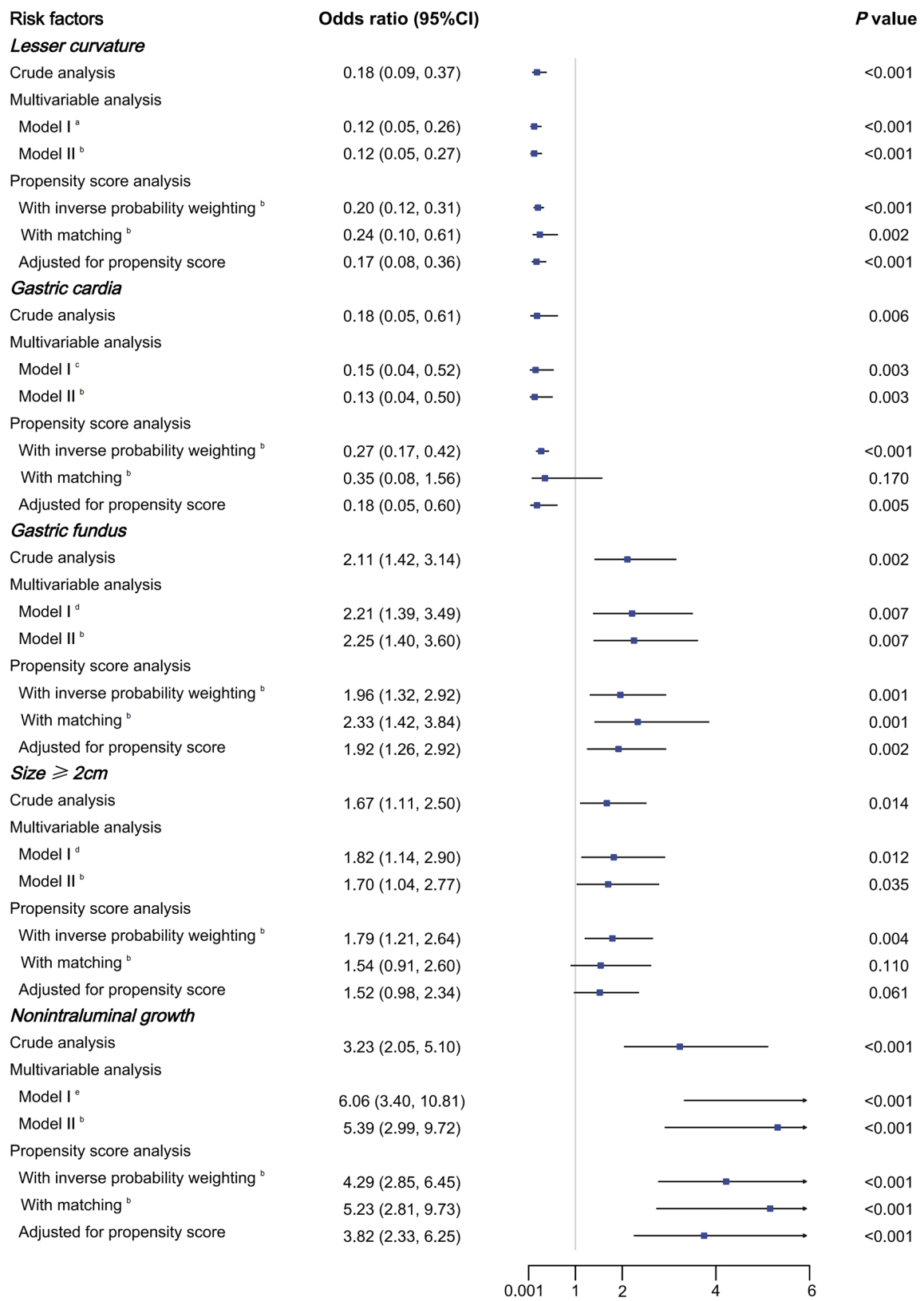


Fig. 5 The effect size of risk factors for perforation in crude univariable, multivariable, and propensity-score analyses. **a** Adjusts for tumor growth pattern; **b** Adjusts for all other varieties; **c** Adjusts for

circumferential location; **d** Adjusts for age, circumferential location and growth pattern; **e** Adjusts for anatomic location and circumferential location

result of our study was well generalized and could provide evidence for clinical application value.

Iatrogenic perforation is a frequent complication in gGISTs under ER, while perforation during operation was reported associated with secondary infections and sepsis [7, 8]. In this present study a higher incidence of sepsis, a longer time until start of oral intake, longer postoperative hospital stays and higher total cost were identified in patients underwent ER with perforation. Thus, it is crucial to identify the risk factors for perioperative perforation of gGISTs during ER. According to previous studies, the perforation rate ranges 6.7–62.5% [7, 8, 15–18], and varies according to the tumor location, size, and growth pattern [19–21, 45]. Zhang et al. reported that, compared with the body (11.5%), the fundus of the stomach was the site of more perforations (21.5%) of gastric subepithelial tumors during endoscopic excavation. He et al. [45] also revealed that the perforation rate of gastric subepithelial tumors in the fundus (23.4%) was higher than that in the body (4.7%). Kim et al. [7] reported 6 cases of macroperforation in ER group all locating in the fundus or body. However, several other reports observed that the perforation rate of lesions was higher in the body [29, 46]. These conflicting results may be due to two reasons: (1) the heterogeneity of the clinical features of the included patients and endoscopists with varied expertise, and (2) that all previous studies only compared the perforation rate in different groups and did not adjust for potential confounders to calculate the independent effects of tumor location on perforation. In this study, we also found that lesions in the fundus showed a remarkably higher perforation risk than those in other locations, and lesions in the cardia exhibited a lower perforation risk than those in other sites. We collected potential confounders related to the lesions and endoscopists and used comprehensive methods to adjust for these confounders. We found that lesions in the fundus were associated with higher perforation risk (aOR 2.25; 95% CI 1.40–3.60), and those in the cardia were associated with fewer perforations (aOR 0.13; 95% CI 0.04–0.50) via regression analysis, propensity score, and subgroup analysis. The varied perforation risks in different anatomic locations may be a result of the different thicknesses of the gastric walls at these sites.

Multiple studies have explored the association between anatomic location and perforation rate and found that locating in upper third of stomach, especially in gastric fundus, was associated with higher perforation rate [30, 47, 48]. The main reason may be the difficulty in manipulating the endoscope and the thickness of the gastric wall in fundus was thinner than in other locations [49, 50]. Similar result was also confirmed in our study. However, few studies have evaluated the role of the circumferential location of gGISTs. Kim et al. [29] reported that early gastric cancer in the lesser curvature showed a lower perforation rate (1.5%) than other

locations (2.0–5.0%), but no independent association was observed. Suzuki et al. [51] found that early gastric cancer in the greater curvature manifested a higher perforation rate (0.4%) than in other parts (0.1%), although multivariate analysis showed no significant effects. Notably, Ojima et al. [52] reported that gastric epithelial lesions in the greater curvature were an independent risk factor associated with perforation (OR 7.04; 95% CI 3.13–15.80), since the greater curvature had limited visual field and blood retention caused by gravity. Here, we found that gGISTs in the lesser curvature showed a significantly lower perforation risk than those in other locations, which has not been reported before. Multivariate analysis and several sensitivity analyses revealed that lesions in the lesser curvature were an independent protective factor (aOR 0.12; 95% CI 0.05–0.27) for perforation. The lesser curvature of the stomach is where the greater and lesser omentum converge, which provides space for the connective tissue enveloping the serosal layer. According to our previous reports, endoscopic subserosal dissection (ESSD) of submucosal tumors (SMTs) performed in this space is feasible and safe while maintaining the integrity of the serosa and reducing the risk of adverse events [26]. Therefore, gGISTs in the lesser curvature were easier to lift and separate due to the existence of the space for the connective tissue, thus reducing the occurrence of perforation.

We also investigated the effects of tumor size and growth pattern on perforation of gGISTs during ER. Meng et al. [46] found that the perforation rate of gGIST with a large tumor size (> 20 mm, 37.5%) was higher than that of small tumors (≤ 20 mm, 9.1%), but the independent risk effect was not calculated. Ye et al. [19] identified that larger tumor size (OR 1.54; 95% CI 1.07–2.24), extraluminal growth (OR 1.77; 95% CI 1.01–3.11), and extensive connection to the MP layer (OR 10.47; 95% CI 5.00–21.93) were independent risk factors for perioperative perforation of upper gastrointestinal SMTs, including 250 gGISTs. Ye and Xu et al. [12, 20] reported similar results for SMTs treated with ESTR and found that lesions with larger tumor size and extraluminal growth showed a higher perforation rate. However, all these studies included other histological types of SMT, while GISTs tended to have more perforations compared with other histological types [12, 21, 53]. In the present study, size ≥ 2 cm (aOR 1.70; 95% CI 1.04–2.77), and non-intraluminal growth pattern (aOR 5.39; 95% CI 2.99–9.72) were associated with higher perforation risk of ER for gGISTs, consistent with these previous studies on SMT [12, 53]. Gastric GISTs with non-intraluminal growth patterns and larger tumor sizes are often difficult to resect endoscopically [14]. Although several novel methods have been established to successfully resect these gGISTs *en bloc*, perforation is difficult to avoid due to the limited surgical space and relatively thin gastric wall [31, 54]. We noticed

that experienced endoscopists could achieve a lower perforation rate in non-intraluminal gGISTs (OR 0.37; 95% CI 0.17–0.84; data not shown). This indicates that these lesions should be managed by experienced endoscopists to reduce complications.

Despite the large sample size and sufficient sensitivity analysis, this study had some limitations. First, because of the nature of this single-center retrospective study, selection bias could exist. Thus, we performed multiple sensitivity analyses of the PS to minimize bias and evaluate the dependent effect of each risk factor. Second, because intentional perforation is needed in certain cases to achieve complete resection, it is challenging to distinguish the two types of perforation (accidental perforation during ESD and needed perforation performed by EFTR) for the nature of our retrospective study. To minimize bias, we excluded all cases that underwent EFR-C with intentional perforation [24]. Third, as we excluded the cases with incomplete resection to reduce the bias of perforation, the results were not applicable to incomplete resections and the risk factors associated with incomplete resection were not evaluated. Future studies will focus more on incomplete resection. Finally, the sample size and events of the extraluminal group were insufficient to perform a detailed subgroup analysis; thus, we combined the groups into non-intraluminal growth patterns. Nevertheless, our study provides sufficient information to establish a more precise endoscopic management strategy for gGISTs.

Conclusions

This study identified that tumors in non-intraluminal growth patterns, with a larger size, and located in the fundus are independent risk factors, while located in the lesser curvature or cardia are independent protective factors for perforation of gGISTs during ER. This study provides evidence for more precise endoscopic management strategies to minimize perforation of gGISTs under ER.

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Author contributions The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. Conception and design: MN, LW; Development of methodology: DT, WR; Acquisition of data: RM, JY, PY; Analysis and interpretation of data: XD, GX, YL, HY, MC; Writing, review, and/or revision of the manuscript: MN, DT, WR; Study supervision: GX, YL, HY, MC, LW.

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Data availability All researchers can submit a request to acquire the anonymized data presented in this manuscript from the corresponding author (Lei Wang). The decision to disclose the data will be made by the corresponding author. The data disclosure can be requested for 36 months from the article publication.

Declarations

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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